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Grant Award N00014-14-1-0028

DEVELOPMENT OF MEDICAL TECHNOLOGY  
FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS  
INTERIM RESEARCH PERFORMANCE REPORT  
SUBMITTED JULY 11, 2014

Office of Naval Research

And

The National Marrow Donor Program®

3001 Broadway Street N.E.

Minneapolis, MN 55413

## **I. Heading**

PI: Dennis L. Confer, M.D.

National Marrow Donor Program

N00014-14-1-0028

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

## **II. Scientific and Technical Objectives**

The main objective of this grant is to develop, test and mature the ability of the National Marrow Donor Program<sup>®</sup> (NMDP) to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents, primarily ionizing radiation or chemical weapons containing nitrogen mustard. An accident, a military incident, or terrorist act in which a number of individuals are exposed to marrow toxic agents will result in injuries from mild to lethal. Casualties will be triaged by first responders, and those with major marrow injuries who may ultimately be candidates for hematopoietic cell transplantation (HCT) will need to be identified. HCT donor identification activities will be initiated for all potential HCT candidates. NMDP-approved transplant centers will provide a uniform and consistent clinical foundation for receiving, evaluating and caring for casualties. NMDP coordinating center will orchestrate the process to rapidly identify the best available donor or cord blood unit for each patient utilizing its state-of-the-art communication infrastructure, sample repository, laboratory network, and human leukocyte antigen (HLA) expertise. NMDP's on-going immunobiologic and clinical research activities promote studies to advance the science and technology of HCT to improve outcomes and quality of life for the patients.

## **III. Approach**

### **A. Contingency Preparedness**

HCT teams are uniquely positioned to care for the casualties of marrow toxic injuries. The NMDP manages a network of centers that work in concert to facilitate unrelated HCT. The Radiation Injury Treatment Network (RITN), comprised of a subset of NMDP's network centers, is dedicated to radiological disaster preparedness activities and develops procedures for response to marrow toxic mass casualty incidents.

### **B. Development of Science and Technology for Rapid Identification of Matched Donors**

Disease stage at the time of transplantation is a significant predictor of survival, decreasing the time to identify the best matched donor is critical. Methods are under development to rapidly provide the best matched donor for HCT.

### **C. Immunogenetic Studies in Transplantation**

Improving strategies to avoid and manage complications due to graft alloreactivity is essential to improve the outcomes of HCT. Research efforts are focused on strategies to maximize disease control while minimizing the toxicity related to alloreactivity in HCT.

#### D. Clinical Research in Transplantation

Clinical research creates a platform that facilitates multi-center collaboration and data management to address issues important for managing radiation exposure casualties. Advancing the already robust research capabilities of the NMDP network will facilitate a coordinated and effective contingency response.

### IV. Concise Accomplishments

- a. Contingency Preparedness
  - i. Hired Federal Emergency Management Agency (FEMA) Certified Master Exercise Practitioner as an Exercise Coordinator - Planning 3 exercises
    - 1. New York City (NYC)-NY State Radiological Disaster - tabletop exercise
    - 2. Minneapolis-full scale exercise
    - 3. Dana Farber Cancer Institute – full scale exercise
  - ii. Invited to join the National Alliance for Radiation Readiness-Public/Private Partnership for readiness (NARR)
- b. Development of Science and Technology for Rapid Identification of Matched Donors
  - i. Registry models clinician-focused manuscript accepted in New England Journal of Medicine.
  - ii. Enhanced the performance of the Haplogic donor search algorithm reducing time to generate haplotype frequency updates from 2-3 weeks to <10 hours.
  - iii. Received Best Case Study award at American Society for Histocompatibility and Immunogenetics (ASHI) annual meeting for an analysis of Deoxyribonucleic Acid (DNA) stability on buccal swabs and dried blood samples following prolonged room temperature storage. Results supported a transition to frozen buccal swab storage.
- c. Immunogenetic Studies in Transplantation
  - i. Received Best Abstract award at annual Bone Marrow Transplant (BMT) Tandem Meetings for updated Human Leukocyte Antigen (HLA) matching analysis in >8000 cases (submitted to Blood).
  - ii. Published 6 peer-reviewed manuscripts.
- d. Clinical Research in Transplantation
  - i. Revised and released 26 electronic clinical data collection forms in FormsNet system. The revised forms are critical to ensure data collection reflects changes to clinical practice.

## V. Expanded Accomplishments

### Contingency Preparedness

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*Maintain the Radiation Injury Treatment Network (RITN) to prepare for the care of patients resulting from a hematopoietic toxic event.*

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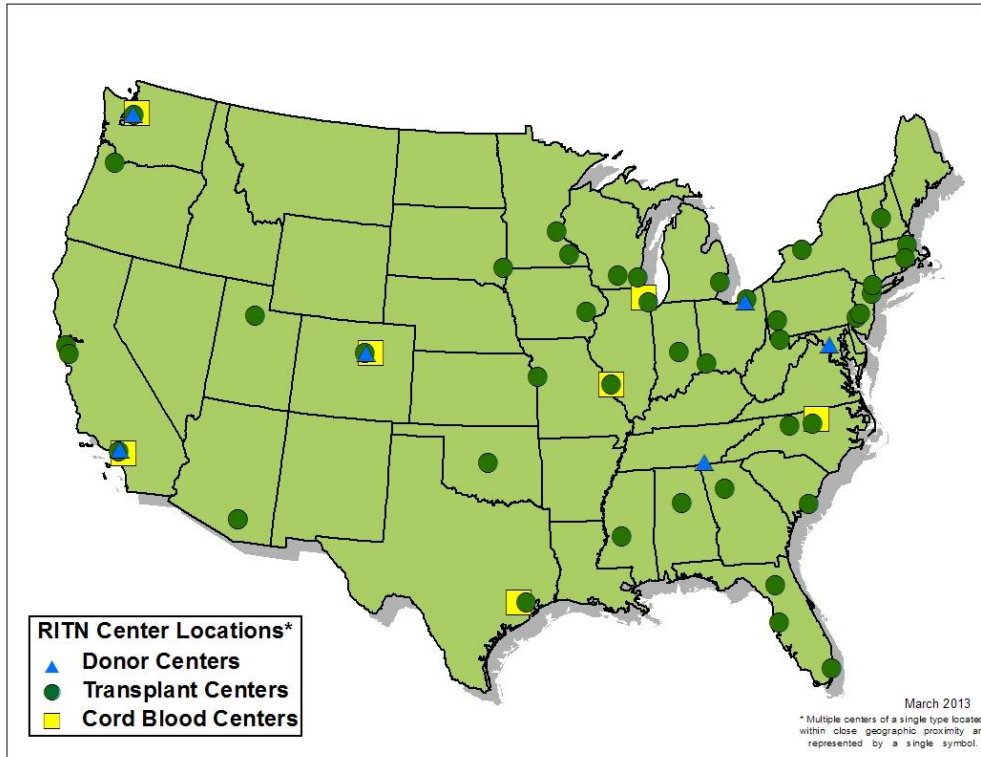
During the performance period, the NMDP continued to develop the RITN by:

- Conducting site assessments
- Facilitating tabletop exercises
- Releasing new web based training:
  - Intro to RITN
  - RITN Concept of Operations
  - Government Emergency Telecommunications System (GETS) 101
  - Satellite telephone 101
  - Non-medical Radiation Awareness Training
- Funding a full-scale radiological incident exercise at Mayo Hospitals and Clinics
- Holding two web based tabletop exercises for 17 hospitals
- Coordinating the first RITN sponsored mobile Radiation Emergency Assistance Center/Training Site (REAC/TS) advanced medical training course at Duke University
- Coordinating two resident REAC/TS advanced medical training courses
- Forming new partnership with CMCRs
- Holding the 4th biennial RITN educational conference w/ 175 attendees

This long list will be discussed individually and in depth in the following sections.

Invitations sent to hospitals to join RITN begin with confirming their participation in both the NMDP Network of treatment centers as well as the National Disaster Medical System (NDMS). The NDMS is comprised of over 1,800 accredited hospitals across the nation that have agreed to receive trauma casualties following a disaster. The program is managed by the Department of Health and Human Services. As a result of this targeted recruitment, three new transplant centers joined RITN; unfortunately, one center was lost due to attrition, resulting in a total composition of: 55 transplant centers, 6 donor centers, and 7 cord blood banks (Fig. 1). The new centers that joined RITN are:

1. Boston Children's (Boston, MA)
2. All Children's (FL)
3. Thomas Jefferson (Philadelphia, PA)



*Figure 1. Location of RITN Centers*

RITN centers were asked to continue to develop their level of preparedness. Tasks included communications drills, updating of standard operating procedures, outreach to local public health and emergency management contacts, a tabletop exercise and training of staff.

During the period of performance, 98% of RITN centers completed all of these required annual tasks (Fig. 2). This is in alignment with the previous year; to ensure this happened additional options to complete the annual training tasks were offered.

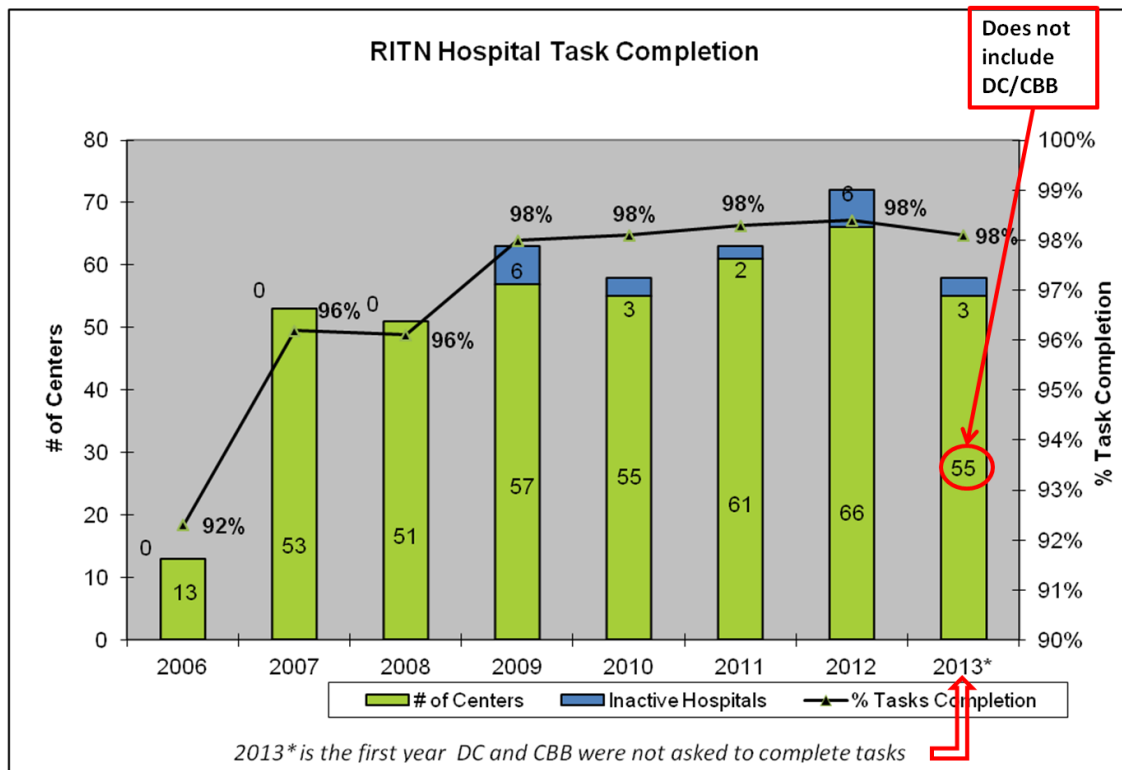


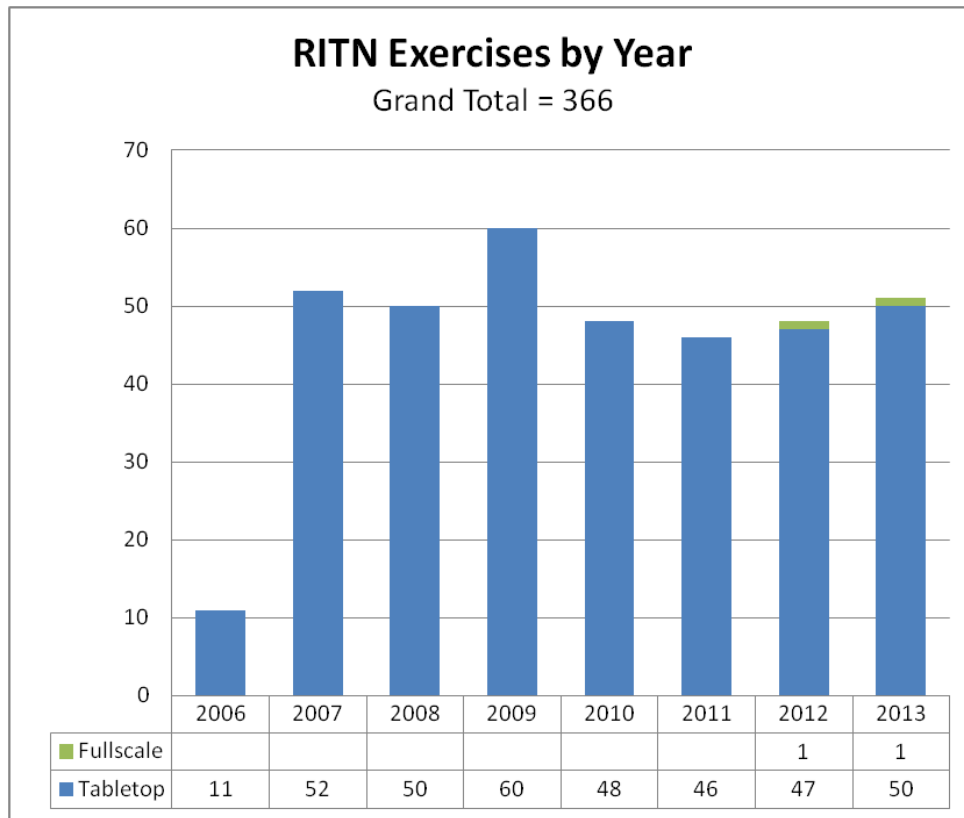
Figure 2. RITN Center task completion by year

**Tabletop exercise task:** The 2013 tabletop exercise presented the detonation of multiple Radiological Exposure Devices placed across the US resulting in thousands of casualties with Acute Radiation Syndrome. The exercise was very well received by all RITN centers, particularly the opportunity to participate in the exercise via an internet webinar that was facilitated by the RITN Control Cell. Hospitals commented that this allowed all of their staff to participate versus having a key person step out and run the exercise for them as well it was noted that the ability to hear from peer hospitals about how they would respond and what they have in place was very insightful. This afforded the opportunity for the participants to see best practices, affirm consistent practices and issues among peers. Since this was the first year where a web based exercise was offered it was limited to 17 participating hospitals. The number of RITN centers participating in tabletop exercises annually is summarized in figure 3.



<b>Summary of RITN TTX Scenarios</b>		
<b>Year</b>	<b>Scenario</b>	<b>Max Victims</b>
2006	Radiological Exposure Device (RED) placed on public train system	650 identified as having some level of Acute Radiation Syndrome (ARS). 50 patients to each center
2007	Train derailment spills multiple chemicals, produces vapor cloud which exposes a crowd of 15,000	5,000 (mostly children and senior citizens)
2008	IND was detonated and 300,000 victims were triaged	5,000 victims required RITN assistance
2009	10-kiloton nuclear device detonated in a major metropolitan center	12,000 patients with high radiation dose in the 200-600 rad range. 300 patients to each center
2010	Detonation of a surface burst 10-kiloton nuclear device in major metropolitan center	20,000 patients with high radiation dose in the 200-600 rad range. 500 patients to each center
2011	National Disaster Medical System (NDMS) flow and integration	Not specified
2012	1 kT IND detonated 500 miles away from RITN center, 20 patients to prioritize using provided casualty cards	20 casualty cards w/ limited bed availability provided
2013 w/ Webinar Option	Radiological exposure devices placed on mass transit vehicles in multiple US cities	4,500 casualties nationwide; 300 patients and 140 family members are sent to each RITN center
2014 Primarily Webinar (planned)	Detonation of a 1kT Improvised Nuclear Device (IND)	100 patients from a large metropolitan area 500 miles away

*Table 1. List of annual RITN tabletop exercise scenarios and level of patient surge.*



*Figure 3. Number of RITN centers participating in exercises from 2006-2013.*

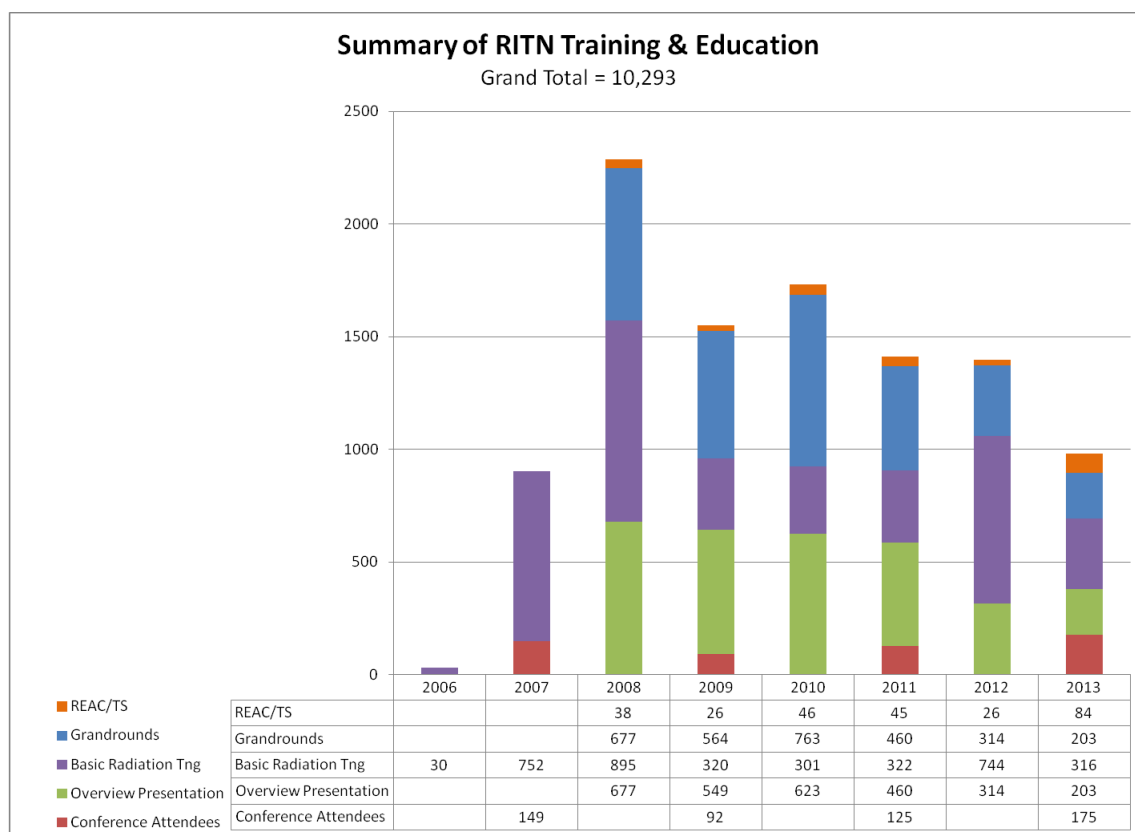
**Training task:** Training options have expanded as RITN has grown. As shown in Figure 4, centers can now choose between conducting Basic Radiation Training, sending a physician to the REAC/TS training, conducting an Acute Radiation Syndrome Medical Grand rounds session, and having a site assessment conducted. In addition, centers can conduct community outreach/education through presentation of the RITN Overview Presentation. All of these materials, except REAC/TS training, are available unrestricted, through the RITN website. In 2013 five more web based training courses were released bringing the catalog to include:

1. Introduction to RITN
2. RITN Concept of Operations
3. GETS 101
4. Satellite telephone 101
5. Basic Radiation Training (BRT) (released in 2012)
6. Non-medical Radiation Awareness Training

The online system allows RITN center staff to complete the full course at their own pace and receive an electronic certificate of completion after meeting all the course objectives including knowledge assessments.

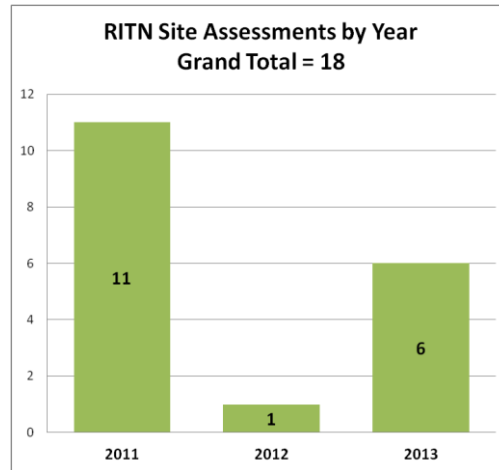
RITN continues to educate the medical community through conferences held every other year, and each has been rated very successful by attendees:

- 2013 – Mitigating Radiation Damage (held in partnership with Center for Medical Countermeasures Against Radiation (CMCR)) (175 attendees)
- 2011 – State of the Science Workshop: Radiation Exposure, Medical Countermeasures and Treatment (125 attendees)
- 2009 – Medical and Organizational Challenges Resulting from a Radiological/Nuclear Emergency (130 attendees)
- 2007 - Nuclear Terrorism: Preparedness and Response for Hematology/Oncology Centers (100 attendees)



*Figure 4. RITN center staff training accomplished by year.*

In 2011, RITN initiated the Site Assessment program where a RITN Control Cell staff member reviewed existing documentation at multiple RITN transplant centers using a standardized checklist (figure 5). Areas evaluated included Casualty Processing, Outpatient Treatment of Casualties, Inpatient Treatment of Casualties, Coordination with City, State and Regional Assets, and Documentation.



*Figure 5. RITN center site assessments by year.*

Using the fields in the Site Assessment Checklist the standard operation procedure (SOP) template was updated and all centers updated local SOPs using the new template.

The RITN continuously seeks to formalize the partnerships developed with federal agencies and organizations.

Memoranda of Understanding (MOU) are established with the following groups to collaborate on preparedness efforts:

- American Society for Blood and Marrow Transplantation (ASBMT) since 2006
- Department of Health and Human Services – Office of the Assistant Secretary for Preparedness and Response (HHS-ASPR) since 2007
- American Association of Blood Banks (AABB)-Disasters Task Force since 2008
- New England Center for Emergency Preparedness (NECEP) since 2010
- European Group for Blood and Marrow Transplantation - Nuclear Accident Committee (EBMT-NAC) since 2011

Additionally, the RITN maintains and develops informal relationships to increase awareness about RITN worldwide through close interaction with:

- Biomedical Advanced Research and Development Authority (BARDA)
- Health Resources and Services Administration (HRSA)
- World Health Organization - Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN)
- Radiation Emergency Assistance Center and Training Site (REAC/TS)
- Armed Forces Radiobiology Research Institute (AFRRI)
- National Institute of Allergy and Infectious Diseases (NIAID)

- National Institutes of Health (NIH) - National Library of Medicine (NLM) - Radiation Emergency Medical Management (REMM)
- American Hospital Association (AHA)
- American Burn Association (ABA)
- Association of State and Territorial Health Officials (ASTHO)
- National Association of City and County Health Officials (NACCHO)
- Veteran's Administration Health System
- Centers for Medical Countermeasures Against Radiation (CMCR)
- National Security Council staff

RITN receives at no cost, access to Health Care Standard<sup>®</sup> (HCS<sup>®</sup>) software through a partnership with the developer Global Emergency Resources. This software allows the RITN to consolidate participating hospitals Capability Reports and to communicate situation status updates to the network through a web based interface. Annual tests are conducted to ensure that users are familiar with the system and that it is capable of receiving and consolidating submitted data.

The Assistant Secretary for Preparedness and Response from the Department of Health and Human Services has been a partner since the foundation of RITN. This partnership is formalized through an MOU and is prominently displayed on the Department of Health and Human Services website for Public Health Emergencies on the Chemical, Biological, Radiological, Nuclear and Explosive Branch page, (<http://www.PHE.gov/about/oem/cbrne>, and below):



Figure 6. Chemical, Biological, Radiological, Nuclear and Explosive Branch webpage noting the partnership with RITN.

In February 2012, the RITN Executive Committee released the RITN Concept of Operations. This document established a uniform understanding among RITN center staff and non-medical RITN partners of the anticipated participation of RITN centers during a national disaster. The Concept of Operations describes the triage and flow of casualties from the initial catastrophic incident through the disaster aftermath to the treatment facility, establishing a basis for all RITN centers to work from as they plan for their part in the response to a national disaster. Included in the Concept of Operations are new estimates of expected casualties for the RITN network of centers from a 10kT Improvised Nuclear Device, casualty flow diagram, and an estimated timeline of the response to an incident. Two important outcomes of the creation of this document have been the Conceptual Flow of Victims to a RITN Center, which has assisted conversations between RITN centers and their local public health agencies, as well as the development of the estimated casualty breakdown mentioned earlier that projects that 70% of the casualties will require outpatient monitoring with some supportive care, 25% will require inpatient care with various degrees of supportive care, and at most 5% will be candidates for HCT.

***NMDP's critical functions must remain operational during contingency situations that directly affect the Coordinating Center.***

During 2013 and 2014 (to date), the NMDP further improved its resiliency through the Operational Continuity Plan (OCP). The 2013 OCP exercise validated the ability of selected specialized staff to transfer and conduct NMDP Kitmaker operations at a recovery site and to systematically offload some Kitmaker activity to the Department of Defense (DoD) Kitmaker as part of the continuity of this critical task. Exercise objectives included Repository staff relocating to the contingency site and establishing connectivity to StarLink production, Repository staff building and sending production kits for one day from the contingency site, DoD Kitmaker staff at DoD site successfully establishing connectivity to StarLink production, and DoD Kitmaker staff building and sending NMDP production kits for one day from DoD site.

The exercise results proved satisfactory. The NMDP Kitmaker Team received an exercise message to relocate to Broadway Ridge REM004 to continue their critical function. The NMDP Kitmaker Team successfully built and sent 44 kits. The DoD Kitmaker Team received an exercise message to assume NMDP Kitmaker activity and successfully built and sent 33 kits. Kit types included Confirmatory Typing (CT)-Infectious Disease Markers (IDM), IDM Only, IDM-PRE, IDM-RSH, IDM-RSH-PRE, RSH Only, High Resolution (HR), DR, PRE Only, and CT Only. The exercise identified several areas for improvement and recommended changes incorporated into a corrective action plan.

In 2013, NMDP executed a planned system shutdown of major information systems in order to execute a scheduled system upgrade. Pre-outage activities included determining resource availability to identify manual work requirements, identifying department teams who determined which tasks would be done manually and which tasks would be deferred, developing electronic control documents, identifying and addressing dependencies between departments, developing tracking mechanisms to document work that had been performed manually, gating incoming electronic messages to avoid losing data during shutdown, clearing patient-driven queues before shutting down, and preparing for a system rollback if the upgrade was unsuccessful. Staff successfully implemented manual processes for over 120 hours. Network partners were aware of the planned event and transplant activity continued uninterrupted.

Other OCP support activities included aligning NMDP plans with the requirements specified in International Organization for Standardization (ISO) 22301:2012 to ensure compliance with industry standards, updating the OCP, the business continuity response team, and critical task lists. The emergency communications system components (satellite telephones, GETS cards, and the mass telephonic alert system) were maintained and tested. The Operational Continuity Steering Committee reviewed changes and additions to the Critical Task List at their annual meeting. The committee is co-chaired by the Chief Medical Officer and the Strategic Development Officer and seated by the Chief Information Officer; Chief Financial Officer; Senior VP, Legal, Risk and Network Affairs; and the Senior VP, Operations.

## **Development of Science and Technology for Rapid Identification of Matched Donors**

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### **Increasing the resolution and quality of the HLA testing of volunteers on the Registry will speed donor selection.**

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#### *Increased diversity of newly recruited donors*

During the NMDP's FY14 to-date (Oct 1, 2013 to April 30, 2014), NMDP donor centers (including Department of Defense (DoD)) and recruitment groups recruited 105,105 minority race and 111,305 Caucasian donors for a total of 216,410 U.S. donors added to the registry. Navy funding supported the HLA typing of 100,462 donors (excluding DoD), of this culturally diverse group (55% minority). These numbers continue to accumulate with current funding and the summaries for the FY14 progress will be reported at the end of October 2014.

#### *Advancing technology improved performance and pricing*

The NMDP increased the number of donors receiving typing at HLA-C, DQB1, DQA1, DPB1, and DPA1 typing at recruitment. Since April 2014, all new donors are typed at minimum of HLA-A, B, C, DRB1, DQB1, and DPB1 at a higher-than-intermediate level of resolution.

To maximize the effect of the additional typing, a process is in place to strategically select specific newly recruited donors, based on donor demographic data, and direct their recruitment samples to specific laboratories for 6 locus (HLA-A, B, C, DRB1, DQB1 and DPB1) typing by NGS technology. The goal is to capture the donors most often selected by transplant physicians, specifically young males, and ensure that they are listed on the registry with the best possible resolution and number of loci tested. This is particularly critical during times of a contingency where well HLA-characterized adult donors can be readily matched to patients in need of HCT for ARS.

#### *Two-Step Recruitment at Live Drive Registration*

In order to further our understanding of donor personal commitment and its effect on downstream donor availability, the NMDP piloted a 2-step donor recruitment study. The hypothesis is that those who pro-actively take a second activation step will be more committed to being on the registry and available if called. Several thousand live drive recruits were asked to take an additional step to activate their membership, in order to have their sample typed and to be listed on the registry. Much like credit card activation, the new recruit was required to call in to an automated phone line, text in an activation confirmation, or enter an activation confirmation online. Results are under evaluation, and will be completed in Fiscal Year (FY) 14 with follow-up studies of availability rates of those who activated and outreach to those who did not activate.



## *DNA Acquisition Methods Provide a Stable Sample Source*

### Sample Storage Research Study

<b>4 Year Time Point – 2011</b>	<b>5 Year Time Point – 2012</b>
HLA Typing: <ul style="list-style-type: none"><li>• 100% accuracy for whole blood</li><li>• 100% accuracy for filter paper</li><li>• 100% accuracy for buccal swabs</li></ul>	HLA Typing: <ul style="list-style-type: none"><li>• 100% accuracy for whole blood</li><li>• 99% accuracy for filter paper</li><li>• 97% accuracy for buccal swabs</li></ul>
DNA Quantity: Sufficient for testing	DNA Quantity: Sufficient for testing
DNA Quality: Buccal swab DNA showing degradation <ul style="list-style-type: none"><li>• 5 swabs (17%) needed repeat testing</li></ul>	DNA Quality: Filter paper samples showing degradation, Buccal swab DNA showing more degradation than in 2011 <ul style="list-style-type: none"><li>• 14 filter papers (47%) and 24 swabs (80%) needed repeat testing</li></ul>

*Table 2: Results for the buccal swab stability study*

Results show that DNA degradation issues first seen in Year 4 are tending to increase in Year 5, with buccal swabs showing degradation earlier than blood spotted onto filter paper. The study was presented at the November 2013 annual meeting of the ASHI, and was recognized with the award for ‘Best Stem Cell Case Study’. The study prompted re-evaluation of the NMDP Repository storage model and led to the development of the frozen swab storage strategy that is currently being implemented.

### Frozen Buccal Swab Storage

Be The Match Registry member samples stored at the Repository provide the basis for Customized Typing requested on behalf of patients, for rapid testing in the event of a national disaster, and for prospective registry enrichment typing. The transition from controlled room temperature storage to frozen storage at -30°C has been designed to preserve the long-term utility of this valuable resource.

A feasibility study evaluated the use of Frozen Buccal Swabs, as an alternative to controlled room temperature buccal swab storage. Results showed that DNA quality, quantity and high-resolution typing were unaffected by the freezing process. The use of frozen storage to maintain the long-term stability of buccal swabs is also being used by another registry after they

experienced failures in Class I by sequence-based typing for buccal swabs stored at room temperature for five or more years. A new 40 year storage study is underway to evaluate the long-term ability to obtain accurate high resolution HLA typing with sufficient quality and quantity of DNA from stored frozen buccal swabs.

When fully implemented, incoming samples will follow 2 paths:

- Two swabs stored at controlled room temperature, for initial registry typing (for easy access).
- Two swabs stored frozen, for long-term registry needs (for long-term sample preservation).

### Preservative Treatment for Buccal Swabs

In addition to freezing buccal swabs, other avenues of sample preservation are being investigated. One option is the use of simple treatments for maintaining DNA integrity on buccal swab samples stored at room temperature. An initial feasibility report was prepared by an external consultant and covered current methodologies and potential approaches requiring further research. Further investigation is underway and will form the basis for defining a testing design.

### Alternate Sample Collection Methods Study

In an effort to evaluate the suitability of alternate sample collection methods, a limited feasibility study was initiated in 2010 to gain a broader understanding of varying sample collection and storage methods currently in the market, including possibilities for storage formats that offer increased sample lifetime, more compact storage, and greater downstream sample utility for further detailed typing. In particular, the potential to store samples or DNA in a format conducive to storage over the 40 year period that many members remain on the registry is an attractive possibility and would ensure that material is available for evaluation when needed for a searching patient or a contingency event.

- Sample sets were collected from 15 volunteer donors for evaluation. Each donor collected samples using:
  - Oragene DNA saliva sample collection kit from DNA Genotek
  - Collect Eject Project (CEP) Swab, an ejectable-tip buccal swab from Fitzco, Inc., composed of cotton-based fibrous material in a matrix format
  - Standard NMDP cotton-tipped buccal swab on polystyrene shaft
- Samples were sent to 3 laboratories for analysis of the following attributes:
  - Quality and quantity of DNA
  - High resolution typing at HLA-A, B, C, DRB1, DQB1, and DPB1
  - Extraction and processing of DNA for dry storage in GenTegra tubes from GenVault/IntegenX
- Baseline results showed that all 3 sample types provide DNA of sufficient quality and quantity to obtain accurate high resolution HLA typing results at all loci tested. Results also showed variations in quantity, purity, and ease of use.
  - All collection methods produce good quality DNA for HLA typing from fresh samples, with all labs obtaining high resolution typing results at all loci that were consistent with prior testing.

- The disadvantages of CEP-Swab, from both the donor and laboratory perspective, appear to outweigh any potential benefits. For laboratories, the CEP-Swab ejectable tip was convenient to use compared to the need to snip the shaft of the standard swab, but the high absorbency of the tip made processing difficult and likely contributed to lower DNA yields. Donors reported that the material was abrasive and that the swab tip had a tendency to separate from the shaft and disintegrate during swabbing.
- Abundant high-quality DNA was obtained from the Oragene saliva samples, but DNA purification steps were time-consuming for laboratory staff and donor satisfaction scores were low for the saliva collection methodology,
- Extracted DNA from each of the sample collection methods was stored in a dry, room temperature stable state in GenTegra tubes and a Whole Genome Amplification product (WGA) was obtained from each.

In FY14, stored samples were sent to laboratories for high resolution HLA typing, and results are under evaluation comparing original 3-year stored samples, extracted-GenTegra-DNA, WGA-GenTegra-DNA, and WGA-frozen-DNA.

#### *Enhancing Non-HLA Data for Selected Donors*

##### Enrich registry data with donor Cytomegalovirus (CMV) and/or ABO information

Transplant centers utilize donor CMV status and blood type (ABO/Rh) as non-HLA selection factors when multiple equally well matched donors are available. Currently the only process to obtain this information is to request the potential donor on behalf of the patient, obtain a fresh blood sample, and perform IDM tests that include the donor blood type and presence/absence of circulating antibodies to CMV. Two cost-effective alternative approaches have been considered.

For CMV, a saliva sample was considered. This would be more cost-effective than a blood sample, as the saliva sample could be self-collected and mailed by the donor, therefore avoiding the cost of arranging a phlebotomy appointment and paying the draw site provider.

- CMV testing from saliva samples is unlikely to be suitable to allow a correlation to presence/absence of CMV Antibody. A 2013 study by Descamps, et al using the Oragene saliva kit showed that CMV shedding was insufficient for PCR assay detection.

ABO/Rh testing is more likely to be feasible for a significant number of registry members than CMV, and would have a similar benefit in providing early information to increase donor utilization and speed the search process for some patients.

A working group was formed to investigate multiple channels for acquiring registry member ABO Rh information for registry listing prior to determination of blood type via multiple avenues:

- ABO/Rh at Recruitment by DNA-based testing: Due to recent advances in testing methodology (primarily due to Next-Generation Sequencing), it has become feasible to explore adding ABO/Rh as another locus that could be tested from the same sample at the same time as recruitment HLA testing. The NMDP has made sets of 1000 blind samples available to laboratories for validation testing. Assessment of concordance between genetic ABO/Rh result and known serological ABO/Rh result will be key for determining suitability for display on the registry.
- ABO/Rh + CMV from a blood sample prior to CT: This service is being piloted in FY14 with a few transplant centers. Initiated by TC request for specific donors, this approach uses a fresh blood sample. Since project launch in January 2014, 9 TCs are participating in the pilot, 66 donors have been requested on behalf of 22 patients, with 29 draws/tests completed.
- Member self-reported blood type at various points of contact with the member beginning at registration. Initial work understanding the number of NMDP donors who are confident they know their ABO-Rh type has been performed (see below).

In FY13, the NMDP performed a study of 50 employees to identify the feasibility of using a simple ABO Rh home test kit for enrichment of registry data for selected members. There is an Food and Drug Administration (FDA) licensed home ABO test kit produced by Eldon Biologics that was evaluated for donor experience and methods for receiving the test kit back from the member, either through sending a photo of the result card through email or mailing the test card to the NMDP repository. Eldon Biologics has performed multiple validation tests to demonstrate the test kit's accuracy. This study showed the Do It Yourself (DIY) ABO kit is feasible for potential donor use, however the manufacturer instructions were not clear enough to get consistent lay public use and getting a picture of the card readout was preferable to a donor returning the card for reading. This option allows some scalability, however it requires more logistics than getting ABO Rh information from a genotyping method. This activity is now in progress and would be preferable to DIY ABO Rh testing.

#### *Quality of HLA typings improved*

The NMDP's comprehensive quality control program has supported the successful increase in the quality of HLA typing received through the contract laboratory network. In addition, this program helps to ensure the accuracy of data obtained from research studies that support abstracts and publications. Blind Quality Control (QC) samples are added to each weekly shipment of new donor recruitment samples. These QC samples comprise 2.5% of each shipment and are indistinguishable from the other samples. The Research Sample Repository contains

frozen cells from thousands of fully HLA-characterized donors and recipients. The majority of QC swabs are created by the Repository staff from expanded B-Lymphoblastoid cell line (LCL) (B-LCL) vials chosen from this resource. The immortalized B-LCLs are applied to cotton-tipped swabs and included as QC in shipments of buccal swab donor samples. With the help of this grant, there are more than 500 B-LCL Masters in active rotation, with over 95% of common well-documented (CWD) alleles represented. The goal of this program is the ability to send a unique QC Master to the high volume laboratories every 8 weeks, with complete coverage of all CWD alleles.

In an effort to decrease the cost and increase the sustainability of the QC program, alternate sources of material that would yield more cost-effective types of QC swab samples were investigated. One of these alternate types is purified genomic DNA absorbed onto cotton-tipped swabs (“DNA-swabs”). This alternative QC sample type has the potential to expand allelic coverage and diversity of HLA in the QC program by utilizing stored NMDP volunteer QC donor blood and Registry donors with desirable HLA types. A pilot study to assess the feasibility of using purified DNA as a new QC sample source was initiated.

Following successful typing results from the pilot study, the purified DNA swabs were incorporated into the regular recruitment and customized shipments to confirm all the contract HLA laboratories could accurately type blind purified DNA QC samples. All labs successfully typed QC samples created from DNA extracted at 2 labs without repeats.

The final phase of the pilot study was to select 5 distinct volunteer QC donors and obtain fresh blood, to assess whether DNA yield is impacted by sample age or freeze/thaw cycles. Five ml of fresh blood, fresh frozen blood, and existing frozen blood inventory were sent to the DNA extraction lab for quantitative and qualitative DNA analysis. No significant difference in yield between the 3 blood sample types for any donor was observed. Based on the results of the study, existing volunteer QC donors with stored repository blood aliquots will be selected for DNA extraction in FY14 for inclusion in the NMDP buccal swab QC program as a substitution to B-LCL swabs.

NMDP has actively engaged network cord blood banks to acquire units that are not deemed suitable for banking in an effort to increase the diversity of cord blood material for the cord QC program. In the last year, the units available for use in the cord QC program has nearly doubled the total number and expanded allelic diversity. NMDP will continue this approach with the goal of increasing allelic diversity and number of unique units available.

#### *Additional Projects to Ensure Quality of HLA Data*

Following the success of the review of rare allele typing and the identification of alleles which were incorrectly typed, this project has moved to the evaluation of less common alleles reported in the Be The Match Registry. Review of HLA results of less common alleles reported to the

NMDP on adult volunteer samples revealed typings that were suspicious and may have been incorrectly reported due to various reasons including:

- Typing methodologies used to report the allele were problematic resulting in a correction of some of the allele results
- Allele reportings of the allele were more prevalent prior to 2002 than are currently being reported.
- Presence of two less common alleles in a donor typing
- Primary data interpretation doesn't match the uncommon allele reported
- Allele reported in a race not documented for the reference cell in the ImMunoGeneTics (IMGT)/HLA database.

Samples were identified using the above rules and retyped by Sequence Specific Oligonucleotide Probes (SSOP) technology. A subset of the SSOP results was confirmed by Sequence Based Typing (SBT) to ensure accuracy. The results of this retyping project to date are summarized in Table 3.

*Table 3: Summary of the less common allele retyping project*

	Samples typed	Confirmed by SBT	Confirmed by SSOP	Changed	% changed
Total	1379	158	270	951	68.96%
HLA-A	392	39	42	311	79.34%
HLA-B	306	34	69	203	66.34%
HLA-DRB1	681	85	159	437	64.17%

These projects also identify problematic alleles that become candidates for inclusion within the NMDP QC program.

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**Primary DNA typing data can be used within the Registry to improve the quality and resolution of volunteer donor HLA assignments.**

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During the performance period the following activities occurred:

- The Primary data interpretation process was re-engineered for flexibility and performance

- A new database model was developed for storing interpretation results
- The primary data interpretation algorithm was re-factored for performance and optimized to the point where 20 million results can be analyzed in less than one day
- Persistence implementations for the Silver Standard genotype list RESTful web service were implemented, deployed, and performance tested at <http://gl.immunogenomics.org>. This allows storage and transmission of HLA allele ambiguities without using human-curated letter ambiguity codes.
- A Toolkit for Immunogenomic Data Exchange and Storage (TIDES) was developed with collaborators as a proof-of-concept cloud-based tool for managing typing data including a database for data queries, Common Gateway Interface (CGI) upload, and format transformation. An alpha-version of TIDES has been deployed on the Amazon cloud (<http://tides.immunogenomics.org>). The next step in this effort is to pilot its use with clinical labs.
- Staff participated in multiple HL7 Working Group Meetings on working groups for Clinical Genomics, Structured Documents, and Orders & Observations. The Genetic Testing Report passed Draft Standard for Trial Use (DSTU) balloting. Work continues in the effort to develop constrained CDA (clinical document architecture) for reporting HLA typing.
- Discussions and collaboration continued with National Center for Biotechnology Information (NCBI) staff to develop use of NCBI GTR (Genetic Testing Registry) for meeting Silver Standard principles for methodology reporting of HLA typing. Agreements have been signed between NCBI and One Lambda with the goal of including One Lambda typing protocol descriptions into NCBI GTR as the first HLA platform to use this new standard resource.
- Requirements were gathered and development of Histoimmunogenetics Mark-up Language (HML) 1.0 specification was initiated. This is a new message format for reporting HLA that includes better support for GL Strings, GTR and cloud storage of primary data for Next Generation Sequencing (NGS).
- The design and implementation of a scalable NGS processing pipeline system was started. This system will be to store and analyze variant effect predictions from NGS reads.

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**Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor or cord blood unit.**

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Data analysis was completed for the ancestry questionnaire pilot (AQP) project. Results from 1752 participants generated the following findings which were summarized in a manuscript that is currently under review in the Journal of the American Medical Association:

- Although there was no clear ‘winner’ in the complex process of self identification in the U.S., knowledge of grandparents’ ancestry was the single most informative data point in characterizing genetic ancestry.
- Nearly 20% of responses were inconsistent between reporting race/ethnicity versus biogeographic ancestry.

- Despite strong concordance between ancestry informative markers (AIMs) and HLA, no measure of self-identification shows complete correspondence with genetic ancestry.
  - In certain cases biogeographic ancestry reporting matches genetic ancestry not reflected in race/ethnicity categories, but in other cases biogeographic ancestries are inconsistently reported, and less informative.
  - When respondents assign ancestry to grandparents, we observe sub-groups of individuals with well defined genetic ancestries, including important differences in HLA frequencies, with implications for transplant matching
  - Collection of donor grandparents' information will improve the chances of finding matches for many patients, particularly from underrepresented groups and mixed-ancestry individuals.
- Work continued analyzing patterns of linkage disequilibrium for the HLA-DPA1 and HLA-DPB1 haplotypes in non-Caucasian populations groups. This data will support matching and modeling efforts to meet the demand for analysis of HLA-DP.
  - Changes were implemented to the matching algorithm, based on approval from the NMDP Histocompatibility Advisory Group, to make antigen match grade assignments based on probabilities. This allows the removal of allele codes from the matching equation and the constraints on the allele code system to not allow certain allele combinations.
  - 9-locus US haplotype frequencies were calculated including DQA1, DPA1, DPB1 loci. These are being validation for future extensions of HapLogic™.
  - Improvements were made to the EM (Expectation Maximization) analysis pipeline (to improve re-generation of Haplotype frequencies that are used in matching). The changes reduced run time significantly (<10 hours vs. 2-3 weeks previously) and added validation steps to the process.
  - Designed a measure to evaluate ambiguity contained in HLA typing that takes into account the number of possible non-ambiguous typings as well as the distribution of their likelihoods. The measure, termed typing ambiguity score, ranges from zero to one, one being given to non-ambiguous typing. The typing ambiguity score was applied to a number of simulated datasets, describing HR, Sequence Based Typing (SBT), Sequence Specific Oligonucleotides (SSO), DNA2 and SERO typing methodologies, in order to quantify the average ambiguity being produced in HLA typing using all of the above typing methodologies.
  - The typing ambiguity score was integrated into HaploStats, a web-tool that provides HLA imputation and summary of ambiguous HLA data using population haplotype frequencies.
  - The Search Archive database was implemented. This is a system to store all search results with the current values for each donor and Cord Blood Unit (CBU) (HLA, demographics). This is a foundational Research and Development (R&D) tool to facilitate future donor selection automation work.



- Work progressed toward generating HLA Haplotype Frequencies based on the genomic allele names which will allow the identification of associations that are currently ignored for applications of this data to matching such as:
  - C\*16:01~B\*52:01:02
  - C\*03:03:01G~B\*52:01:02
  - C\*12:02:01G~B\*52:01:01
- Two manuscripts were accepted for publication
  - “HLA Match Likelihoods for Patients Seeking Unrelated Donor Grafts in the U.S. Registry” accepted for publication in the New England Journal of Medicine
  - “Validation of Statistical Imputation of Allele-Level Multi-Locus Phased Genotypes from Ambiguous HLA Assignments” accepted for publication in Tissue Antigens

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**Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.**

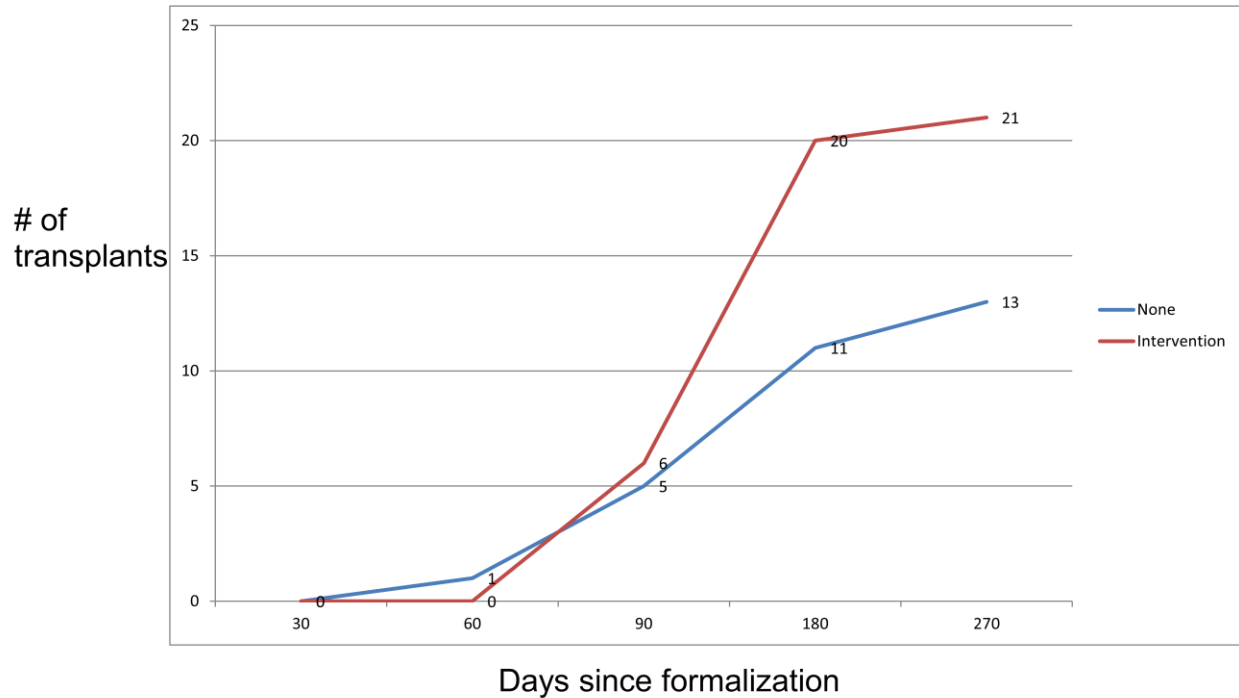
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#### *Donor Match Rate Studies*

The African American (AFA) patient population is the most underserved group in transplantation due to their diverse HLA and donor availability rates. In FY13, The AFA few 10/10 project , was completed under the Office of Naval Research grant, examining all incoming patients from February 2013 to October 2013 to identify a subset of AFA searches that could most benefit from preemptive intervention of NMDP services. Patients who had more challenging searches were randomly enrolled into one of two arms; 182 had intervention, while 178 had no intervention. For the 182 patients in the intervention arm, 2473 donors were selected for pre-emptive contact, and 591 available donors were typed. Ultimately, data on 217 matched and available donors were sent to transplant centers for 115 patients.

Available donors were fully typed at HLA-A, B, C, DRB1 and DQB1, and the transplant center was notified when a suitably matched donor was identified for their consideration. Patients who received this NMDP intervention were more likely to go to transplant with a donor over a cord (64% vs 46%) and achieved a more desirable donor transplant about 60% more often in the intervention group than the non-intervention group (Figure 7).

## Donor transplants



*Figure 7: AFA patients with difficult searches were more likely to identify a donor following NMDP intervention and preemptive screening and HLA typing of donors.*

Removing uninterested donors and typing all potential matched donors helped to clarify enrolled patient searches, thus allowing for a realistic view of their options and helped to remove barriers to transplantation for these underserved patients. Increased consideration of NMDP adult donors appears to have resulted in fewer early transplant center (TC) decisions to move to cord blood unit transplantation for patients. This project was instrumental in understanding the ability for process changes to increase AFA patients getting to transplant, particularly in time of a contingency event.

### *NIH Search Support*

The NMDP collaborated with intramural NIH transplant programs from the National Cancer Institute, the National Heart Lung and Blood Institute and the National Institute of Allergy and Infectious Diseases. These programs are investigating alternative approaches in unrelated donor transplantation to improve patient outcomes. The actual transplants and the investigational portions of each transplant (i.e., the research protocols) are supported entirely with NIH funds. Navy funding supplies support for donor identification, selection and collection. NMDP donors are not research subjects on these protocols because the donors are making standard donations for accepted transplant indications. The research component of these transplants is conducted

entirely by NIH intramural program staff and funded entirely with NIH dollars. The NMDP provided support for the collection of six products (3 peripheral blood stem cells (PBSC), 2 CBU and 1 therapeutic T cell) under current prior grant through April 2014.

*Rapid identification of potential donors for newly diagnosed Acute Myeloid Leukemia (AML) patients*

The Southwest Oncology Group (SWOG) has identified the time from diagnosis of AML to transplant as critical for successful treatment of patients with cytogenetically defined high risk disease. Proceeding to transplant within four months of diagnosis for patients with high risk disease in first chronic remission could potentially improve the overall disease free survival rates. Currently, these patients are referred for transplant following cytogenetic screening and several lines of therapy. The initial diagnosis and treatment phase can take several months significantly delaying the initiation of an unrelated donor search and making transplant within four months highly unlikely. NMDP/Center for International Blood & Marrow Transplant Research<sup>®</sup> (CIBMTR) up front involvement would permit the rapid identification and pre-search screening of potential donors, so patients will be well along in the search process when/if ultimately referred for HCT.

In April 2013 SWOG initiated the clinical trial entitled, [“S1203: A Randomized Phase III Study of Standard Cytarabine plus Daunorubicin \(7+3\) Therapy or Idarubicin with High Dose Cytarabine \(IA\) versus IA with Vorinostat \(IA+V\) in Younger Patients with Previously Untreated Acute Myeloid Leukemia \(AML\)”](#). The trial is a randomized phase III trial of cytarabine and daunorubicin hydrochloride or idarubicin and cytarabine with or without vorinostat to see how well they work in treating younger patients (18-60 years old) with previously untreated acute myeloid leukemia. Drugs used in chemotherapy, such as cytarabine, daunorubicin hydrochloride, idarubicin, and vorinostat, work in different ways to stop the growth of cancer cells, either by killing the cells or stopping them from dividing. Giving more than one drug (combination chemotherapy) and giving the drugs in different doses and in different combinations may kill more cancer cells. It is not yet known which combination chemotherapy is more effective in treating acute myeloid leukemia. The study includes a transplant arm for patients diagnosed with high risk cytogenetics following the initiation of induction therapy (see Figure 8). NMDP/CIBMTR is supporting the project using grant funds to provide study-specific sample collection kits for all enrolled patients, processing samples, HLA typing patients that are diagnosed as cytogenetic high-risk and generating preliminary search strategy reports to assist in the identification of donors and/or CBUs through the NMDP. The resulting search information is provided to the S1203 transplant arm principal investigator who shares the data with the referring physician. During the current period, 73 patients have been enrolled and 26 are diagnosed as high-risk. The time from enrollment to complete search strategy results is 40 days.

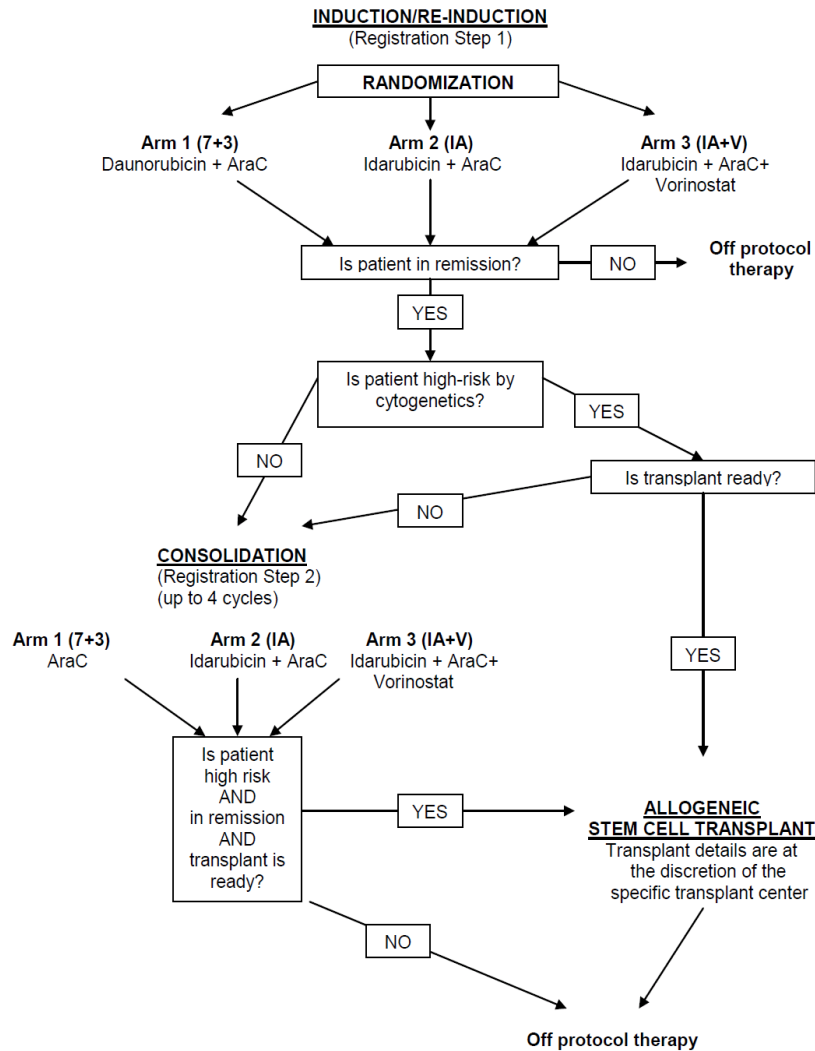


Figure 8. S1203 trial randomization and treatment schema.

## Immunogenetic Studies in Transplantation

**HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations, it will not be possible to delay transplant until a perfectly matched donor can be found.**

### Donor/Recipient Pair Project

A retrospective Donor/Recipient Pair HLA typing project to characterize class I (HLA-A, B and C) and class II (HLA-DRB, DQB1, DQA1, DPA1 and DPB1) alleles of stored donor/recipient paired samples was initiated in 1994. To date, over 15,500 paired samples from the Repository have been fully characterized and the resultant data are available for research use. The data are stored in an NMDP developed database and is available to any researcher with a CIBMTR

approved study wishing to analyze the impact of matching as either the focus of, or as a variable in a research study. To date, over 125 published research studies (not including abstracts) have used these data, including the seminal publication from Lee et al,<sup>21</sup> describing the importance of high resolution HLA matching in unrelated donor transplantation that formed the basis for NMDP's updated guidelines for unrelated adult donor HCT HLA matching.<sup>22</sup>

During FY14, the project initiated testing on an additional 1400 pairs. All samples were selected in collaboration with the CIBMTR Statistical Center to ensure the additional cases would benefit ongoing and future analyses. In addition, the project has added both single and double cord blood transplant pair samples to facilitate studies of HLA matching in this high growth field. Transplantation practices are constantly evolving and the project will continue to enroll the most recent transplant pairs to ensure that changes in practice can be evaluated with fully quality controlled high resolution HLA data. With the implementation of the Immunobiology Project Results (IPR) database, we continue to audit sample groups that contain both KIR and high resolution HLA to allow for inclusion in studies.

#### Donor/Recipient Pair Project KIR

While HLA matching is the most critical genetic determinant of HCT success, studies have found additional genetic determinants that may incrementally impact outcomes – for example, a correlation between KIR B content and relapse-free survival in AML. However, interpretations of association studies are complicated because the underlying haplotypic structures have not been elucidated. In particular, copy number ambiguities need to be investigated further. Only when these haplotypes are understood can more powerful association studies be conducted. More studies are needed to evaluate the roles of non-HLA loci in HCT.

During FY14, Further analysis of KIR haplotypes is continuing by copy number variation typing and algorithm refinement of the pilot project cohort as well as samples from the Donor/Recipient pairs project. In addition, the two pseudo genes 2DP1 and 3DP1 were added to the current typing strategy due to their importance for determination of killer Immunoglobulin-like Receptor (KIR) haplotypes.

NMDP initiated a collaboration with Daniel Geraghty at Scisco Genetics and Pacific Biosciences with the following specific aims:

- Aim 1: Fosmid library construction including content mapping and fosmid isolation.
- Aim 2: DNA sequencing of the fosmid clones using Pacific Biosciences long read technology.
- Aim 3: Determine phase and full haplotype sequences.

### Antigen Recognition Site Mismatching study

Amino acid mismatches outside the antigen recognition site (ARS) (i.e., exons 2 and 3 for HLA class I and exon 2 for class II) are ignored under current HLA matching guidelines with the assumption that these differences are irrelevant. There is little data to confirm or refute this assumption; furthermore, the amount of data needed to form a conclusion is unattainable.<sup>28</sup> In order to provide more information, the ARS allo-reactivity assessment project will provide insight into the allowable percent tolerance of matching needed outside of the ARS.

Initial investigation of the Class II ARS mismatch of DRB1\*14:01 and DRB1\*14:54 and DRB3\*02:01 and 02:02 respectively have produced preliminary results demonstrating two weakly positive and one positive result. Interestingly, all positive results occurred in one direction only, which is DRB1\*14:01 / DRB3\*02:01 against DRB1\*14:54 / DRB3\*02:02. This data from the Class II analysis was presented in an oral abstract<sup>29</sup> at the 2013 EFI conference in Maastricht, Netherlands. Analysis of four Class I ARS mismatches; A\*02:01 and 02:09, B\*44:02 and 44:27, C\*07:01, 07:06 and 07:18 have demonstrated that the selected pairs do not travel on the same haplotypes. The Class I results were presented at ASHI 2013 in Chicago. Haplotype determination, donor selection and HLA typing was performed to allow for confirmation of the original DRB1\*14:01 and DRB1\*14:54 results.

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*Even when patient and donor are HLA matched, GVHD occurs, therefore, other loci may play a role.*

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Table 4 lists currently active CIBMTR/NMDP-supported studies that are conducted on NMDP samples. The CIBMTR/NMDP encourages such collaborative projects and closely monitor them. Such studies are instrumental to understanding the role of non-HLA loci in HCT. The data is obtained and generated via NMDP donor and recipient research samples, along with their outcomes and demographics. The researchers are required to submit the interpreted results of all assays performed on the samples. The data submission requirement ensures that all sample testing yields information that is readily available to the HCT research community for subsequent analysis and eliminates or reduces duplicative testing to preserve resources and sample inventory. These results are stored in the IPR and IIDB databases, and associated with their samples in the Research Repository database.

Non-HLA data is available for use in research studies in a fashion analogous to the Donor/Recipient Pair Project generated HLA data and is made available, when possible, via the NMDP Bioinformatics web site. Data origin will be noted for all information stored, along with relevant citations. Access to the detailed data will be subject to the existing NMDP/CIBMTR data request procedures.

*Table 4 Immunobiology typing projects utilizing NMDP samples and contributing data to the IPR database*

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
NK Cells, Their Receptors and Unrelated Donor Transplant	J. Miller	2300 pairs	KIR	RT-PCR, FACS, SSO, MALDI-TOF	Yes
Survey of Diversity of Immune Response Genes in Unrelated Hematopoietic Stem Cell Transplantation	C. Hurley	40 Pairs	cytokine and KIR	SBT	Yes
Candidate Gene Study to Examine the Impact of Chemokine and Chemokine Receptor Gene Polymorphisms on the Incidence and Severity of Acute and Chronic Graft Versus Host Disease (GVHD)	R. Abdi	1300 pairs	CCL1, CCL2, CCR5, CCR2, CX3CR1	Taqman PCR	Yes
Functional Significance of Killer Ig-like Receptor (KIR) Genes in HLA Matched and Mismatched Unrelated HCT	B. Dupont, K. Hsu	2000 pairs	KIR	SSP	Yes
Functional Significance of Cytokine Gene Polymorphism in Modulation Risk of Post-Transplant Complications	E. Petersdorf	2500 pairs	>30 Immune response genes	Taqman PCR	Yes
Identification of Functional SNPs in Unrelated HCT	E. Petersdorf	3500 pairs	Entire MHC region	Taqman PCR	In Process
Use of Female Donors with Pre-existing Antibody to H-Y Antigen will Result in Robust Serologic Response to H-Y Antigens in Male HSC transplantation Recipients	D. Miklos	288 pairs	H-Y Antigen	ELISA, protein array	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Multiplexed Genotyping of Human Minor Histocompatibility Antigens (mHAg): Clinical Relevance of mHAg Disparity in Stem Cell Transplantation	T. Ellis	730 pairs	mHAg	Allele-specific Primer Extension	Yes
Genetic Polymorphisms in the Genes Encoding Human Interleukin-7 Receptor- $\alpha$ : Prognostic significance in Allogeneic Stem Cell Transplantation	K. Muller	851 pairs	IL-7	Taqman PCR	Yes
The Effect of Non-Inherited Maternal Antigens in Cord Blood Transplantation	L. Baxter-Lowe	102 pairs	HLA	SBT	Yes
Detection of HLA Antibody in Single Antigen HLA-Mismatched Unrelated Donor Transplants	S. Arai, D. Miklos	200 pairs	Anti-body	ELISA, Protein array	Yes
Detection of Donor-Directed, HLA-Specific Alloantibodies in Recipients of Unrelated Stem Cell Transplantation and Their Relationship to Graft/Patient Outcome	R. Bray	111 pairs	Anti-bodies	Flow cytometry	Yes
Genome-wide Association in Unrelated Donor Transplant Recipients and Donors: A Pilot Study	R. Goyal	858 pairs	> 600,000 Genome wide SNPs	Human 610 - Quad V1 arrays	In process
SNPs in the p53 Pathway and Outcomes in URD HCT	B. DuPont	1500 pairs	p53, ATM, MDM2 and p21/Waf1	Taqman	In process



Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Association of Donor and Recipient Gene Polymorphisms of Drug and Innate Immune Response with Outcomes after Unrelated Registry Donor (URD) HCT	V. Rocha	725 pairs	GSTP, GSTT, GSTM, UGT CD14, TIRAP, and NALPs	Taqman	Yes
To Develop and Test a Prognostic Index for Survival in CML URD HCT	A. Dickinson	1100 pairs	TNF, IL-1RA and IL-10	Taqman	Yes
Evaluation of TGF- $\beta$ 1 Promoter and Signal Peptide Polymorphisms as Risk Factors for Renal Dysfunction in HCT Patients Treated with Cyclosporine A	R. Shah	400 samples	TGF- $\beta$ 1	Taqman	Yes
Donor and Recipient Telomere Length as Predictors of Outcomes after Hematopoietic Stem Cell Transplant in Patients with Acquired Severe Aplastic Anemia	S. Gadalla	650 samples	Telomere length and Telomerase Polymorphisms	Taqman	Yes
Development of a GVHD Prevention Biodiagnostic Test	R. Somogyi	450 samples	Gene Expression Array	Array	In process
Genetic polymorphisms and HCT related mortality Re: Pre-HCT conditioning in matched unrelated donor HCT	T. Hahn	>4,000 pairs	GWAS	Array	In process
Impact of CTLA4 SNPs on outcome after URD transplant	M. Jagasia	1,200 pairs	CTLA-4 SNPs	Taqman	Yes
KIR genotyping and immune function in MDS patients prior to unrelated donor transplantation	E. E. Warlick and J. Miller	970 samples	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	In process

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data submitted
Plasma YKL-40 and CHI3LI genotype to predict mortality after unrelated donor HCT	B. Kornblit	800 pairs	YKL-40 plasma levels and CHI3LI SNPs	ELISA and Taqman	Yes
Natural killer cell genomics and outcomes after allogeneic transplantation for lymphoma	V. Bachanova, J. Miller, D. Weisdorf and L. Burns	800 pairs	KIR genotype, expression and cellular function	SSP, flow cytometry and cellular assays	In process
Effect of genetic ancestry matching on HCT outcomes	A. Madbouly, M. Maiers and N. Majhail	2300 pairs	Ancestry Informative Markers	Taqman	In process
Impact of MHC Class I chain related polymorphisms on HCT outcomes	M. Askar and R. Sobecks	700 pairs	MICA genotypes	Taqman	Yes
Impact of donor signal-regulatory protein alpha polymorphism on HCT outcome	A. Gassas, J. Danska and S. Rajakumar	400 pairs	SIRP- $\alpha$ SNPs	Taqman	In process
Discrepancy analysis of microsatellite loci as a proxy measure for ancestral differentiation	J. Harvey, C. Steward and V. Rocha	800 pairs	Microsatellites and STR	Taqman	In process
Prognostic impact of somatic mutation and the levels of CXC chemokine ligands in MDS	W. Saber, R.C. Lindsley and B. Ebert	1300 pairs	Chemokine levels  Somatic mutations	ELISA  Sequence capture	In process
Mitochondrial DNA haplotypes and outcome	M. Verneris and J. Ross	4000 pairs	SNPs	Taqman	In process
Assessing T cell repertoire similarity in HLA mismatched HCT	E. Meyer	50 samples	TCR repertoire sequence	NGS	In process

#### Immunobiology Integration Database (IIDB)

- A service interface was implemented for IIDB to assign HapLogic™ matching results to all historical transplant pairs. This will effectively increase the size of the cohort for studies where HLA typing data is lacking or ambiguous.

- The system to associate race and ethnicity data was re-implemented to address inconsistencies in historical mappings
- The system to process manually entered HLA reported to the CIBMTR on outcomes forms was updated. So far we have processed 96,000 records containing HLA data for analysis. An HLA Validation Service was implemented that applies NMDP Operational rules for the validation of HLA data from CIBMTR forms.
- Additional development occurred on the Immunobiology Integration DataBase (IIDB) application including architectural design for implementing GL Strings instead of NMDP allele codes for representing allele ambiguities.
- Developed process improvements to decrease the daily load-time of Immunological Project Results (IPR) Database by 25%.
- Genetic Typing data for related donors has been incorporated into IIDB

### Clinical Ancestry Study

In support of the Clinical Ancestry outcomes study, a pilot group of 376 samples was genotyped using an ancestry informative markers (AIM) single nucleotide polymorphism (SNP) panel. Preliminary analysis was performed to quantify the genetic ancestry of donors and recipients and estimate the degree of joint co-ancestry among the pairs in the pilot phase. These data were presented in the 2014 CIBMTR Immunobiology Working Committee meeting held during the Bone Marrow Transplant (BMT) Tandem meetings. Multivariate analysis on seven outcomes suggested there are trends worth investigating further. However, most p-values were not significant as the number of donor/recipient pairs in the discovery pilot was small. Four main recipient admixtures were analyzed in the pilot cohort: European American (EUR), AFR, Native American (NAM) and Asian American (ASI). Trends were observed which require a larger sample to show statistical significance. A power analysis was conducted for a second larger phase of the study currently underway.

### Clinical Research in Transplantation

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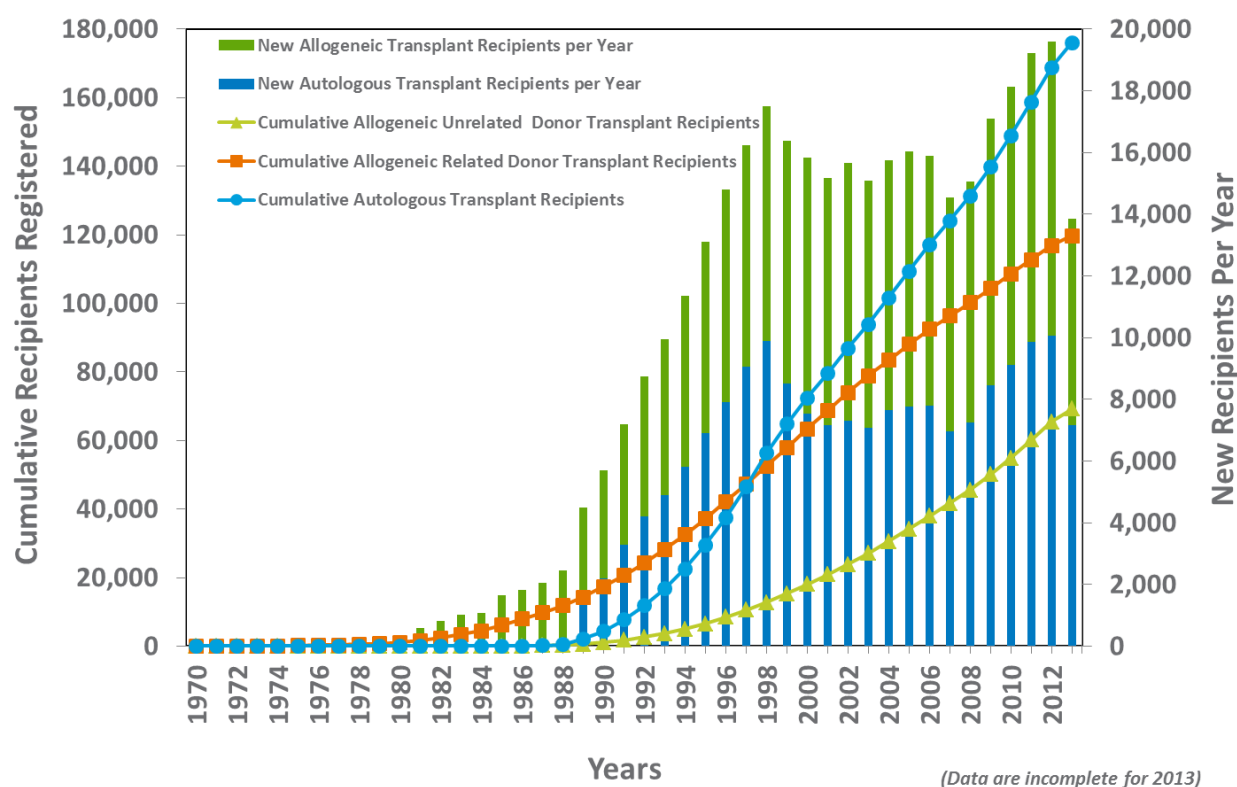
**Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.**

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#### *Observational Research*

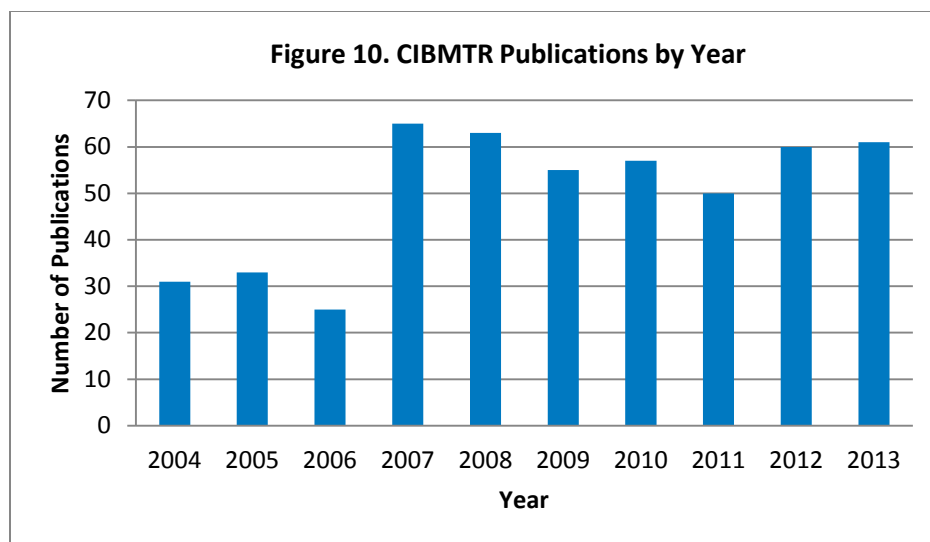
Through the CIBMTR Working Committee structure, which incorporates many highly successful researchers in clinical transplantation, the NMDP expanded its research activities to increase scientific knowledge of blood and marrow transplantation. This was accomplished by performing retrospective studies to identify the most promising transplant approaches, and by identifying the patients most likely to benefit from this therapy. In addition, research in immunobiology was conducted to better understand how transplantation works including how to harness the power of the immune system to control cancer.

The CIBMTR collects data for approximately 19,000 new transplant recipients annually as well as a continually increasing volume of follow-up data on previously reported recipients and donors. Figure 9 shows cumulative accession of transplants since 1970 when the International Bone Marrow Transplant Registry began collecting these data. These data are the basis for the CIBMTR Observational Research program and are accessed by the Working Committees to conduct studies.



*Figure 9. Accession of Transplant Recipients Registered with the CIBMTR*

Currently, there are [15 Working Committees](#) within the CIBMTR with 228 active studies in progress (42 in manuscript preparation and 186 in various states of completion). In 2013, the CIBMTR published a total of 61 peer-reviewed publications (42 working committee studies, 3 Health Services Research, 4 BMTCTN, 4 Statistical Methods and 8 other) (Figure 10). Sources of funding for these studies vary by investigator, but the majority use NMDP resources and CIBMTR statistical support. In addition, the CIBMTR received 156 new study proposals and accepted 88 for discussion at the February 2014 ASBMT/CIBMTR Transplant Tandem Meetings and accepted 46 to go forward to analysis. Twenty five abstracts were submitted and accepted for presentation (17 oral and 8 posters) at the American Society for Histocompatibility (ASH) meeting in December 2013. Fifteen abstracts were submitted and accepted for presentation (12 oral and 3 poster) at the 2014 BMT Tandem Meetings.



### *Clinical Trials*

Since October 2010, the Resource for Clinical Investigation in Blood and Marrow Transplantation (RCI BMT) has been facilitating a study referred to as the Long Term Donor Follow up study. This studies primary goal is to evaluate the hypothesis that the incidence of targeted malignant, thrombotic and autoimmune disorders after unrelated hematopoietic stem cell donation are similar between unstimulated bone Marrow (BM) and filgrastim-mobilized PBSC donors. Once a donor has consented to participate they undergo biennial surveys until study completion which is estimated to be completed by 2020. Cases of targeted disorders are reviewed by the medical monitors to confirm the veracity of the report.

The CIBMTR Survey Research Group (SRG) had responsibility for recruitment of the previously donated donors of which there were a little over 15,000 donors. Through a number of different waves of communication, 66% were reached and responded of which 94% signed consent and enrolled for a total of 9,554 from this cohort. In addition, the Donor Centers prospectively enrolled donors during the work up process. To date, a total of 8,211 donors have enrolled. During the past year, donor centers were given an option of having SRG take over the follow up for enrolled donors. This added nearly 2000 additional donors to the SRG cohort. Of the almost 18,000 subjects currently enrolled, the SRG is responsible for the follow-up assessments of over 11,000 or 62% of the donors.

One of the first studies (07-REV) to be developed within the RCI BMT mechanism completed accrual in 2012 and had an abstract presented as an oral presentation at the 2013 BMT Tandem meetings. In April 2014 a manuscript was accepted in Biology of Blood and Marrow Transplantation entitled, “Lenalidomide Maintenance for High Risk Multiple Myeloma after Allogeneic Hematopoietic Cell Transplantation Biology of Blood and Marrow Transplantation”. A second study, a Phase II, open-label, multi-center, prospective study of double unit umbilical cord blood transplant (UCBT) in adult patients with hematologic malignancies completed accrual in 2011 and data collection late 2012. The study team finalized and submitted a manuscript entitled, “Results of a Prospective Multicenter Myeloablative Double-Unit Cord

Blood Transplantation Trial in Adult Patients with Acute Leukemia and Myelodysplasia”, to the British Journal of Hematology that was accepted pending revisions.

#### *Other Clinical Research activities*

Staff from the RCI BMT continued to work with CIBMTR Information Technology (CIT) staff to explore options for a) comprehensive system for management of activities and studies within the SRG and b) clinical trial management system (CTMS) to coordinate operational and administrative activities within RCI BMT. Full design review processes were completed for both projects. System design work was initiated on the SRG solution using a configurable contact management system. The final decision on build or buy for the CTMS is in late stages of completion.

During this period work continued to provide support to investigator sponsored research when an NMDP unrelated donor was involved. One project, involves data collection from NMDP donors for a study addressing the question if product transplanted from a donor on statin drugs reduces GVHD. A new project was initiated with a pharmaceutical company whose trial involved an alternative method for mobilizing peripheral blood stem cells from the unrelated donor.

#### *Cord Blood research initiatives*

Currently, standards define quality of a CBU through all stages of CBU manufacturing: collection, processing, storage, transport, and infusion. However, about 15-24% of recipients of CBU transplantation do not achieve engraftment. This may, among other factors, be attributable to the quality of the unit which can be negatively impacted at numerous points during manufacture. Recent studies indicate colony forming unit (CFU) and CD34 viability of the highest importance when predicting engraftment.<sup>51,52</sup> Currently the FDA recommends only pre-cryopreservation potency analysis of CBU to ensure quality. However, because cryopreservation and storage can also affect the quality of the CBU, there is evidence to suggest that the addition of post-cryopreservation quality assessment be conducted. The 4th edition of NetCord-Foundation for the Accreditation of Cellular Therapy (FACT) International Cord Blood Standards recommends an additional post-cryopreservation CFU to assess these affects. However, a survey conducted by the NMDP Cord Blood Advisory Group (CBAG) to determine post-cryopreservation/pre-release quality assessment practices of NMDP member cord blood banks (CBB) indicated little inter-bank consensus on the number of and type of assays performed prior to release of the CBU (Table 5). Of the 19 participating CBBs, 84% have established CBU release testing criteria. 53% perform CFU, 47% perform total nucleated cell (TNC), and 37% perform CD34 analysis. 67% perform TNC viability, while 44% perform CD34+ cell viability. A majority (86% of 14 CBBs who answered the question) of CBBs performs overall viability; however, the methodology (7AAD, trypan blue, other) varies between banks. Most CBBs (73%) assay contiguous segments, but 50% do not have a validated segment thaw protocol. Of the 12 CBBs that answered the question of whether they have not released a CBU based on release testing results, 3 (25%) indicated in the positive. Strikingly, the range of what is considered an acceptable result, if defined at all, varied highly between CBBs for the various assays reported.

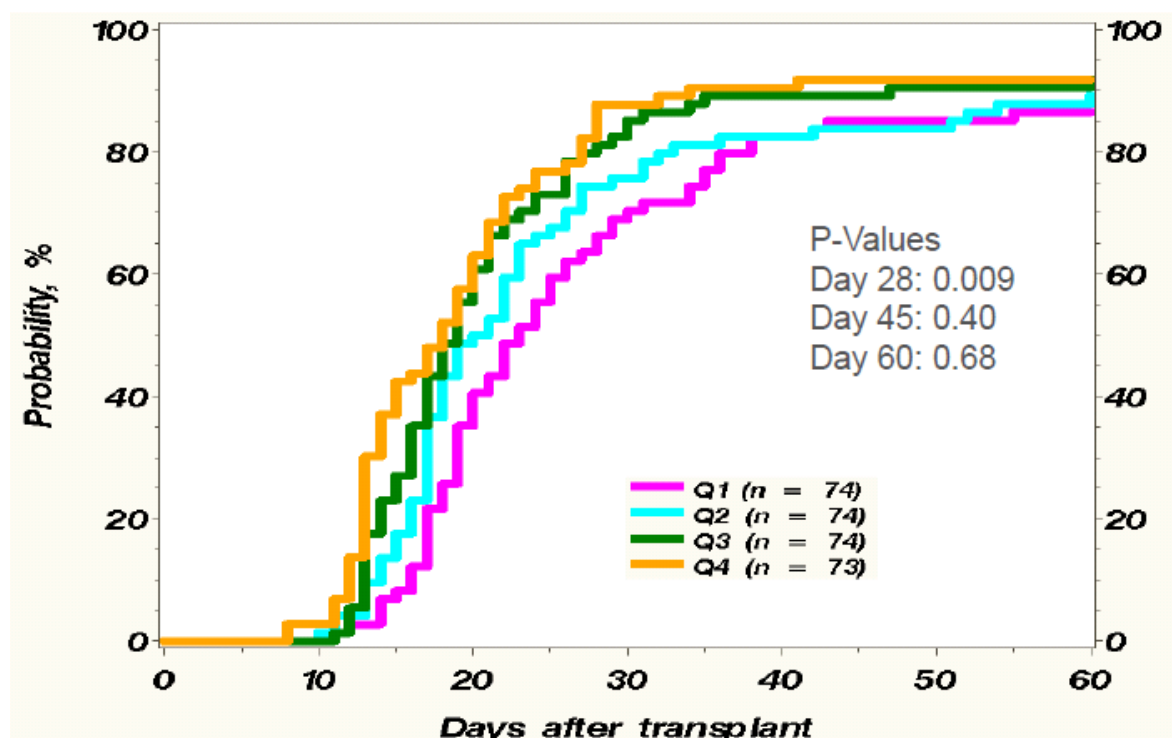
Table 5: CBU release testing criteria practices among NMDP network CBBs

	Parameter		Sample		Sample Handling			Acceptable Results
	Yes (%)	No (%)	Segment (%)	Vial (%)	Thaw (%)	Thaw and Dilute (%)	Thaw and Wash (%)	
<b>TNC Recovery</b>	9 (47)	10 (53)	5 (56)	4 (44)	5 (63)	3 (37)	0 (0)	>50-80%
<b>MNC Recovery</b>	3 (17)	15 (83)	3 (100)	0 (0)	1 (33)	2 (67)	0 (0)	>80%
<b>CD34+ Recovery</b>	7 (37)	12 (63)	5 (71)	2 (29)	4 (57)	2 (29)	1 (14)	>80%
<b>Viability TNC</b>	12 (67)	6 (33)	9 (75)	3 (25)	8 (62)	4 (31)	1 (7)	>40-75%
<b>Viability CD34+</b>	8 (44)	10 (56)	6 (75)	2 (25)	5 (56)	2 (22)	2 (22)	>80-85%
<b>CFU</b>	10 (53)	9 (47)	9 (90)	1 (10)	5 (45)	5 (45)	1 (10)	growth
<b>Other: ALDHbr</b>	1 (6)	16 (94)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	>0.1% CFU

It is therefore important to study the role of post-cryopreservation CBU CFU characteristics on transplant outcomes. The CBAG research sub-committee initiated a study entitled, “Cord blood unit release testing criteria and impact on the transplantation outcome.” The primary aim of the

study was to determine the impact of CBU CFU testing at the time of release on transplantation outcome. The focus of the study was on the CFU assay because post-thaw growth is indicative of overall unit suitability and approximately 50% of NMDP network CBBs perform the assay pre-release. Preliminary results presented at the 12<sup>th</sup> International Cord Blood Symposium in June 2014 showed no correlation between post thaw CFU dose and neutrophil engraftment (figure 11). There was a suggestion that low CFU doses were associated with delayed engraftment by day 28, but the effect disappeared by days 45 and 60 post transplant. The analyses will be finalized in the next several months.

*Figure 11. Cumulative incidence of neutrophil engraftment based on post thaw CFU dose in myeloablative single cord blood transplants for hematological malignancies.*



### *Immunobiology Research*

During a previous grant period, the NMDP developed the Immunobiology Research grant request and award procedures for use by the IBWC and developed the Immunobiology Working Committee (IBWC) Web site

([http://www.cibmtr.org/COMMITTEES/Working\\_Committees/Immunobiology/index.html](http://www.cibmtr.org/COMMITTEES/Working_Committees/Immunobiology/index.html)).

The content was further refined and migrated to the CIBMTR.org Web site in FY10.



During the performance period, grant funds supported significant outreach efforts by the IBWC leadership to increase exposure for the IBWC to basic scientists. The IBWC leadership attended several scientific meetings including: American Society of Hematology, BMT Tandem, European Group for Blood and Marrow Transplant and International Cord Blood Symposium meetings. Support permitted the committee to maintain a strong performance record with 9 publications (submitted or accepted) and collaboration on 3 grants in the current grant year. In addition, 7 new proposals were accepted by the IBWC during the BMT Tandem meetings in February 2014.

IBWC FY14 manuscripts (submitted/accepted):

- Eapen M, Klein JP, Ruggeri A, Spellman S, Lee SJ, Anasetti C, Arcese W, Barker JN, Baxter-Lowe LA, Brown M, Fernandez-Vina MA, Freeman J, He W, Paola Iori A, Horowitz MM, Locatelli F, Marino S, Maiers M, Michel G, Sanz GF, Gluckman E, and Rocha V. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. Published. Blood. 2013 October 18; Epub, DOI:10.1182/blood-2013-05-506253
- Cooley S, Weisdorf DJ, Guethlein LA, Klein JP, Wang T, Marsh SG, Spellman S, Haagenon MD, Saetern K, Ladner M, Trachtenberg E, Parham P, Miller JS. Donor Killer Cell Ig-like Receptor B Haplotypes, Recipient HLA-C1, and HLA-C Mismatch Enhance the Clinical Benefit of Unrelated Transplantation for Acute Myelogenous Leukemia. J Immunol. 2014 Apr 18. [Epub ahead of print] PubMed PMID: 24748496.
- Fleischhauer K, Fernandez-Viña MA, Wang T, Haagenon M, Battiwalla M, Baxter-Lowe LA, Ciceri F, Dehn J, Gajewski J, Hale GA, Heemskerk MBA, Marino SR, McCarthy PL, Miklos D, Oudshoorn M, Pollack MS, Reddy V, Senitzer D, Shaw BE, Waller EK, Lee SJ, and Spellman SR. Risk-associations between HLA-DPB1 T cell epitope matching and outcome of unrelated hematopoietic cell transplantation are independent from HLA-DPA1. Bone Marrow Transplant. 2014 Jun 23. doi:10.1038/bmt.2014.122. [Epub ahead of print] PubMed PMID: 24955785.
- Sengsayadeth S, Wang T, Lee SJ, Haagenon MD, Spellman S, Fernandez-Viña MA, Muller CR, Verneris MR, Savani BN, Jagasia M. Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) Single Nucleotide Polymorphisms Do Not Impact Outcomes after Unrelated Donor Transplant: A Center for International Blood and Marrow Transplant Research Analysis. Biol Blood Marrow Transplant. 2014 Mar 13. pii: S1083-8791(14)00154-2. doi: 10.1016/j.bbmt.2014.03.005. [Epub ahead of print] PubMed PMID: 24631737.
- Gleason MK, Ross JA, Warlick ED, Lund TC, Verneris MR, Wiernik A, Spellman S, Haagenon MD, Lenvik AJ, Litzow MR, Epling-Burnette PK, Weiner LM, Weisdorf DJ, Vallera DA, Miller JS. CD16xCD33 bispecific killer cell engager (BiKE) activates NK cells from MDS patients against primary MDS and MDSC CD33+ targets. Blood. 2014 Mar 20. [Epub ahead of print] PubMed PMID: 24652987..

- Fernandez-Vina M, Wang T, Lee S, Haagenson M, Aljurf M, Askar M, Battiwalla M, Baxter-Lowe LA, Gajewski J, Jakubowski A, Marino S, Oudshoorn M, Marsh S, Petersdorf E, Schultz K, Turner EV, Waller E, Woolfrey A, Umejiego JB, Spellman S, and Setterholm MI. Identification of a Permissible HLA Mismatch in Hematopoietic Stem Cell Transplantation. *Blood*. 2014 Jan 9. [Epub ahead of print] PubMed PMID: 24408320.
- Gadalla SM, Wang T, Haagenson M, Spellman SR, Lee SJ, Williams KM, Wong JY, De Vivo I, Savage SA. Donor Telomere Length Predicts Survival after Unrelated Donor Allogeneic Hematopoietic Cell Transplantation for Severe Aplastic Anemia. *New England Journal of Medicine* (submitted)
- Kornblit B, Enevold C, Wang T, Spellman SR, Haagenson M, Lee SJ, Müller K. Toll-like Receptor Polymorphisms in Allogeneic Hematopoietic Cell Transplantation. *Biology of Blood and Marrow Transplantation* (submitted)
- Pidala J, Lee SJ, Ahn KW, Spellman S, Wang H, Askar M, Dehn J, Fernandez-Vina M, Gratwohl A, Gupta V, Hanna R, Hurley CK, Inamoto Y, Kassim AA, Nishihori T, Mueller C, Oudshoorn M, Petersdorf EW, Prasad V, Saber W, Schultz KR, Storek J, Wood WA, Woolfrey AE, Anasetti C. Non-permissive DPB1 mismatch among otherwise HLA-match donor-recipient pairs results in increased overall mortality after unrelated allogeneic hematopoietic cell transplantation. *Blood* (submitted)

#### IBWC 2014 proposals:

- The prognostic impact of somatic mutations and levels of CXC chemokine ligands on post hematopoietic cell transplantation (HCT) outcomes in patients with myelodysplastic syndromes (MDS). PIs: Wael Saber, Coleman Lindsley, Benjamin Ebert
- Donor-Specific anti HLA antibodies, Allele and Antigen level HLA mismatches in the outcomes of Transplantation of Non-Malignant Diseases with Unrelated Donors. PIs: Marcelo Fernandez-Vina and Ann Woolfrey
- Structural/Functional Models of HLA for Data Mining of Permissive Mismatching in Allogeneic Hematopoietic Stem Cell Transplantation. PI: Loren Gragert
- Indirectly recognizable HLA epitopes (PIRCHES): a retrospective validation study on the role of indirect recognition of mismatched HLA in hematopoietic stem-cell transplantation outcome. PI: Eric Spierings
- A Retrospective Assessment of Outcomes of Follicular Lymphoma Patients who have Undergone Allogeneic Stem Cell Transplant Based on Human Leukocyte Antigen (HLA) Type. PIs: Basem William, Marcos de Lima, Marcelo Fernandez-Vina and Brian Hill

- Assessing the similarity of the T cell receptor repertoire in allogeneic hematopoietic stem cell recipients with the same single human leukocyte mismatches. PI: Everett Meyer
- mtDNA haplotypes and unrelated donor transplant outcomes. PIs: Michael Verneris and Julie Ross

### *CIT Minneapolis Initiatives*

The scope of the work performed by the CIBMTR Information Technology (IT) department in Minneapolis includes collecting and reporting outcomes data on all allogeneic transplantations performed in the U.S. (for the SCTOD, as required by U.S. law). U.S. transplant centers also voluntarily submit autologous transplanation data, and transplant centers worldwide voluntarily submit both autologous and allogeneic transplantation data. CIT strives to provide applications that will reduce center burden for government mandated forms and provide high quality data on demand.

### **CIT Application Suite:**

- FormsNet: Recipient – Donor - Clinical Trials
- A Growable Network Information System<sup>®</sup> (AGNIS<sup>®</sup>)
- Management Reporting
- Sample Tracking
- Auditing

### **FormsNet**

Since its original release in Dec 2007, the Recipient Module of the FormsNet application has been used at more than 399 centers to register 125,019 patients and collect over 773,400 forms with more than 10 million data elements. This program was developed for both local data entry from paper forms and web-based entry by clinical centers. Currently over 92% of the data are being entered by clinical centers via the web. In the last six months, NMDP derived 98% by calculating forms submitted electronically divided by those forms eligible for electronic submission. Two forms (2801 – log of appended documents and 2802 – transfer forms) can only be submitted on paper to ensure audit standards.

FormsNet (FN) is a secure, Web-based application for submission of outcomes data to CIBMTR(Recipient module), support for Donor clearance, follow-up and safety (Donor module), and support of electronic data capture for RCI-BMT Clinical Trials (Clinical Trials module). The original features of real-time error validation and override capabilities, and the option to generate a Forms Due Report to track all forms due for every patient have been improved and enhanced. The original deployment in December 2007 was built in 126,000 lines of code supporting 90 Recipient forms and no user tools. Today there are over 1 million lines of code supporting 242 forms, tools, web services, email, and three user-based modules. The

application is fully integrated with the CIT applications suite supporting CIBMTR. The application was converted from its original website to a web application with an enhanced object oriented code structure. Service Oriented Architecture integration services were created to provide flexibility and extensibility for future enhancements. In FY12, the planned upgrade to FormsNet, replaced the technical foundation of the current FN2 application, with more agile, efficient & effective systems. It enhances the user experience by providing enhanced functionality (defined by the network users). In FY 2014, the Donor module was upgraded to the FormsNet 3 platform providing the same benefits for Donor module users as realized by Recipient module users. The top objectives achieved were:

- Enhance Performance –improved speed, usability, consistency and usefulness of forms access, user data entry, and validations
- Improved user experience/usability –offer real-time data validations, rules, control of data entry “flow”, error handling and messaging, and “smart navigations” (from form-to-form or from field-to-field on the same form), auto population of key fields
- Improved data quality- enable data entry to be as easy, consistent, accurate, and fast as possible
- Productivity / Process Improvement - decreased the time it takes to add a new form or add a validation.

CIBMTR IT supported the CIBMTR Forms Revisions process with major revisions for 26 Recipient forms. These revisions aligned data collection forms with current treatment practices, provided significant new functionality to improve user experience and improved overall data quality. This release was part of FY14’s focus of improving overall user satisfaction; other accomplishments included a performance release of FormsNet in late FY13, and a series of site visits to 22 transplant centers across the country. The performance release improved FormsNet 3 performance up to 50% in key areas of the application as well as providing enhanced printing functions. The site visits enabled CIBMTR to better understand each center’s needs, and provided a mechanism to gather ideas on how to enhance communication, training, and applications.

### **RITN electronic data collection**

As part of the RITN preparedness efforts, Institutional Review Board-approved protocols are in place at multiple RITN centers for the collection of demographic, situational and clinical data from radiation casualties who are sent to RITN hospitals and provide informed consent. The CIBMTR is uniquely positioned to collect this data, based on the existing data collection system and the program’s long track-record of collecting similar data on more than 22,000 blood and marrow transplant recipients annually. Importantly, the data collection approach for radiation casualties will differ from that which is collected daily in CIBMTR centers since only those who receive a transplant are tracked in the current system. This data collection process will not only capture those who undergo blood and marrow transplantation but also all radiation casualties treated at RITN centers and provide informed consent. The data obtained from the RITN Data Collection Interface will be an invaluable resource for subsequent efforts to improve triage, treatment and monitoring approaches for individuals exposed to radiation.

In FY14, CIBMTR performed analysis and design to support the RITN data collection needs. This included confirming the overall scope, interviewing key stakeholders, identifying business needs/requirements, defining required forms and other key design elements essential to begin development early in FY15.

## **AGNIS**

AGNIS is a system for electronic messaging of standard Common Data Elements (CDEs) between participating nodes. Messaging can occur between transplant centers, registries, investigators or any combination of entities willing to map relevant data elements and install the software/messaging system. The system relies on two key components, data standards in the form of CDEs, and software for transferring the data, providing audit trails, conveying error messages, etc.

- CDE Development:  
CIBMTR has invested substantial effort defining CDEs for CIBMTR forms. All CDEs are defined in the Cancer Data Standards Repository (caDSR) of the National Cancer Institute (NCI). This leverages a strong national system of standards regarding the definitions and related metadata. Additionally, a substantial portion of the CDEs have also been defined in the Biomedical Research Integrated Domain Group (BRIDG) model, which is compatible with HL7, the most prevalent ‘language’ used in biomedical informatics.
- caDSR:
  - Definitions have been created for more than 2,800 CDEs associated with more than 8,300 data points on 80 forms.

The following 15 Recipient outcome forms have been released in the caDSR and are available for electronic data exchange via AGNIS: seven mandated forms (pre- and post-Transplant Essential Data (TED), HLA, IDM, Infusion, Chimerism, and Selected Post-TED ), five Comprehensive Forms (Baseline, 100 day Follow-Up, 6 mo. to 2 yr. Follow-up, Annual Follow-Up, and Death), Unique ID Assignment, and two disease specific inserts (Pre- and Post-HSCT Hodgkin and Non-Hodgkins Lymphoma).

- BRIDG:  
Definitions have been created for more than 1900 CDEs on 38 forms, including the TED level data forms: Pre-TED, Post-TED, HLA, Infectious Disease, and Infusion forms.

#### System Users:

- Independent Transplant Centers:
  - 4 centers actively submitting data through AGNIS: H. Lee Moffitt, MD Anderson, Cleveland Clinic, and Stanford
  - 4-6 centers actively developing solutions
  - 2 centers considering RED cap database solutions
- Transplant centers using Vendor solutions:
  - 18 centers have been authorized to submit and retrieve all AGNIS supported forms using Remedy Informatics' software.
  - 43 centers working with StemSoft to submit and receive all AGNIS supported forms from CIBMTR
  - 2 centers authorized to submit and retrieve all AGNIS supported forms via Organ Transplant Tracking Record (OTTR) software
  - 1 center authorized to submit and retrieve all AGNIS supported forms via Mediware software
  - 2 additional vendors developing software: Raystech and MSA

#### System Enhancements:

To date in FY14, the AGNIS team accomplished the following:

- The AGNIS platform was used for over 13,000 submissions to FormsNet
- Provided ongoing support for EBMT-CIBMTR and CIBMTR-Eurocord AGNIS connections
- EBMT has submitted > 8000 initial forms and is beginning to send follow-up forms for those transplants (for 50 centers)
- Released new ticketing system for request and issue management, held user forum at the ASBMT Tandem Meetings, now support 7 new form revisions, initiated design for the core AGNIS processing engine improvements, provided enhanced tools, improved mapping support for centers, and additional support for submission of comprehensive report forms.
- Registry connections:
  - EBMT has been working with the CIBMTR to develop a pathway to share TED-level data from EBMT centers that also participate in the CIBMTR. Mapping has occurred for the Pre-TED, Post-TED at 100 days, Unique ID, and Infusion forms. Data submission, initially manually and now with automation, has occurred for participating centers who have not submitted forms to CIBMTR since 2008 for new transplants.

- This approach has provided over 9,000 new form records.
  - With automation, expect to receive about 40,000 Pre-TED, Post-TED, Unique ID and Infusion forms
  - The U.S. Immunodeficiencies Network (USIDNet) is an outcomes registry for Immune deficiencies sponsored by the NIAID that has a database system that has been re-constructed in the last few years. CIBMTR collaborates for a prospective study and in that context USIDNet obtained small amount of funding to collect outcomes data for patients with Immune Deficiencies from CIBMTR through AGNIS. CIBMTR provides requested data to USIDNET on an annual basis.
- EMR connections:  
CIBMTR worked with EPIC to integrate 18 standard CDEs into the BMT registration form in EPIC (BMT smartform) in 2012-3.

## Information Management

The CIBMTR Information Management Strategy (IMS) project's main objective is to establish a comprehensive program for the management of data across the enterprise, turning the large volumes of data into a strategic asset supporting high value, sophisticated analyses. The Data Warehouse is the primary deliverable for this project. At delivery, the Data Warehouse will contain high quality, validated data readily available to researchers for immunobiology, outcomes, and other types of analyses. CIBMTR operational teams will be able to dramatically reduce the amount of time they spend on data consolidation, preparation, and validation of datasets and instead focus on the analysis. As a result, analyses will be completed in a timely manner facilitating decision-making based on these data assets.

This effort is aligned with NMDP enterprise architectural standards. The first deliverable implemented an Integrated Data Store (IDS) which serves as the foundation for the long-term data warehouse. Using the IDS as the unified data source, the first phase of the Data Warehouse has been completed by integrating data used for immunobiology analyses into the Data Warehouse. Table 13 below shows the types of data stored in the Data Warehouse and their original data sources:

*Table 13. Types of sources of data in CIBMTR Data Warehouse*

Focus area	Description	Source
<b>IDM</b>	<ul style="list-style-type: none"> <li>• Donor IDMs information for NMDP facilitated HCTs</li> </ul>	Legacy (Formsnet1) & current FormsNet3

Focus area	Description	Source
<b>Infusion data</b>	<ul style="list-style-type: none"> <li>50 most Requested Variables for ad-hoc and center volumes reporting requests from FN3</li> <li>Clinical outcome data tied to each infusion event (future)</li> </ul>	FormsNet3, SIP
<b>Research Specimen Data</b>	<ul style="list-style-type: none"> <li>Research Repository Specimen Inventory data on related and unrelated cords, donors, and recipient samples</li> <li>Data on Research Repository Specimen submission and compliance</li> </ul>	BIO Res (IPR/RR)
<b>NMDP Source Data</b>	<ul style="list-style-type: none"> <li>Cord Blood Unit Data</li> <li>Double Cord (Multi)</li> </ul>	StarLink CordLink (SyBase) Emtrax through Reg ODS
<b>HLA/KIR Match Data</b>	<ul style="list-style-type: none"> <li>Transformed CIBMTR Legacy HLA data</li> <li>HLA data for donor/recipient for NMDP facilitated HCTs, legacy and current (STAR/SIP) (form 2005)</li> <li>HLA data transformation on new form 2005/non-NMDP Tx SCTOD data</li> <li>Donor-Recipient Match Grade results (HLA Save)</li> <li>KIR data</li> <li>Re-Evaluate current data sources</li> </ul>	<ul style="list-style-type: none"> <li>CIBMTR OBS DB</li> <li>STAR</li> <li>FormsNet3</li> <li>IPR</li> <li>HLA Save</li> </ul>
<b>Donor &amp; Recipient data</b>	<ul style="list-style-type: none"> <li>Transformed Donor and Recipient data</li> <li>Provides self service environment for analysis through pre-defined joins (business view of the metadata), calculations and generating adhoc data sets</li> <li>Capability for near real time(~ 5 minutes) data sharing and analytics across forms through combined and unified virtualization layer (views)</li> <li>Faster turnaround on visibility to data quality fixes.</li> </ul>	<ul style="list-style-type: none"> <li>FormsNet3</li> </ul>
<b>Metadata</b>	<ul style="list-style-type: none"> <li>Provides data lineage, impact analysis and FormsNet metadata analysis</li> </ul>	<ul style="list-style-type: none"> <li>FormsNet Metadata, BODI metadata, OBIEE metadata</li> </ul>
<b>Center volumes</b>	<ul style="list-style-type: none"> <li>Provides metrics around the number of infusions by center/donor type/product type/disease/age group/race variables</li> <li>Replaces existing manual process</li> </ul>	<ul style="list-style-type: none"> <li>FormsNet, NMDP</li> </ul>



In addition to the referenced source data consolidated in the Data Warehouse, CIT has also developed, in the last 9 months, the following functionality that is dependent on the data from the Data Warehouse.

- Expanded automated processes to capture center transplant activity and volumes reporting Dashboards for Donor research and adhoc reporting capability
- HLA and match grade variables for use in studies
- Metadata and impact analysis capabilities across multiple data sources
- Support for resolution of HLA errors on Form 2005

## **VI. Work plan**

### **a. Contingency Preparedness**

- Increase the number of hospitals participating in the RITN.
- Have RITN hospitals complete radiological preparedness tasks to maintain their status.
- Further develop partnerships with government agencies.
- Hold multiple Fullscale or Functional exercises at RITN centers.
- Implement an exercise and evaluation program staffed by an exercise specialist.
- Continue to train RITN staff through mobile REAC/TS training.
- Further increase visibility of RITN through funding a radiological preparedness project with a national public health association.

### **b. Development of Science and Technology for Rapid Identification of Matched Donors**

- Expand the genetic diversity of the Registry through continued addition of adult donors and cord blood units, utilizing high volume HLA typing methodologies.
- Evaluate the suitability of buccal swabs as a method to collect DNA samples to HLA type casualties and potential related donors in contingency situations, and to obtain research samples.
- Evaluate the factors of donor utilization and speed of search process after strategic upgrading of selected adult volunteer donors.
- Maintain a comprehensive quality control program for all contracted HLA typing projects.
- Enhance systems to store and interpret primary DNA typing data to improve the quality and resolution of volunteer donor HLA assignments.
- Utilize HLA allele and haplotype frequency data to improve the donor selection algorithm.

### **c. Immunogenetic Studies in Transplantation**

- Complete HLA and KIR typing on additional donor/recipient transplant pairs to support evaluation of clinical studies of HLA mismatched transplants in an attempt to define tolerable mismatching in the unrelated donor HCT setting.
- Identify and recruit volunteer donors to the ARS project to investigate the impact of mismatches outside of the ARS.

- Continue to collect and archive genetic testing data collected on samples tested through NMDP/CIBMTR research project
- Complete the testing on the full cohort of the Clinical Ancestry Study and prepare the datafile for analysis.
- Change – will not pursue the full MHC typing project and will focus efforts on completing retrospective typing using established methods for HLA typing through the DRPP. Exploration of alternative NGS typing methodologies to evaluate the impact of complete HLA gene matching is planned under the FY15 work plan.

d. Clinical Research in Transplantation

- Continue to conduct observational research studies through the 15 working committees of the CIBMTR. Efforts are focused on finalizing publications from the studies completed to date in FY14 and finalizing analyses for the submission to the ASH and BMT Tandem annual meetings.
- The Survey Research Group will continue to conduct donor follow-up assessments for the Long Term Donor Follow-up study.
- Complete the preliminary analyses for the post-thaw CFU cord blood engraftment study and continue to recruit additional cases for analysis.
- Develop and release FormsNet enhancements to improve system performance, user experience, data quality and forms development turnaround time.
- Continue development and execution of the CIBMTR Information Management Strategy project.

**VII. Major Problems/Issues (if any)**

No major problems encountered to date.

**VIII. Technology Transfer**

No technology transfer to report.

**IX. Foreign Collaborations and Supported Foreign Nationals**

NMDP has no sub awards with nor is it collaborating with any foreign entity or foreign national under this grant.

**X. Productivity**

a. Refereed Journal Articles

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- c. Books or Chapters – None to report
- d. Technical Reports – None to report
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- f. Patents – None to report
- g. Awards/Honors – None to report

## **XI. Award Participants**

<u>Employee Name</u>	<u>Employee Name</u>	<u>Employee Name</u>
Adams, Alexia J	Gragert, Loren A.	Olson, Janelle A
Ahmed, Zubair	Griffith, Claudia R	Olson, Kelli A
Anderson, Emily Ann	Gurung, Karma B	O'Neill, Colleen P
Andreasen, Chelsey J.	Haagenson, Michael D.	Paunic, Vanja
Arnold, James B	Halagan, Michael S	Petroske, Charney J
Aryal, Nirmal N	Halbert, Nicholas K	Pollack, Jane F
Averill, Diane E	Hauck, Angela M.	Proue, Mandi A
Ayim, Jack O	Hayes, Ellyce A	Puligundla, Gangadharam P
Barker Jr, James K	Hays, Amy E.	Radloff, Gretchen A
Bauer, Miranda M	Henry, Jessica L	Roe, David D.
Beduhn, Elizabeth A.	Hornung, Raymond A.	Roers, Bertram A.

Bellamy, Leslie L	Howe, Kathryn A	Salchert, Yasmina S
Besse, Kelsey L	Huesmann, Naomi R	Schaper, Kirt A
Besser, RaeAnne M.	Johnson, Madeline A	Scheller, Daniel G.
Bies, Amanda L	Jordahl, Charles C.	Schneider, Joel T
Brady, Colleen K	Kemp, Ann	Schneyman, Douglas
Brown, Maria H.	Kempenich, Jane Hart	Smith, Jacob M
Buck, Kelly J.	Kennedy, Caleb J	Somanahalli Giddegowda, Chaitra
Burgess, John W	Kiefer, Deidre M	Spahn, Ashley M.
Campbell, Daniel M	Kloker, Dean R	Spellman, Stephen R.
Case, Jr., Cullen M.	Kobusingye, Hati K	Spiess, Laurie L
Chan, Hang	Kofstad Johnson, Christine C	Stritesky, Gretta L
Chitphakdithai, Pintip	Leahy, Nicole P	Tasky, Sheryl A.
Christianson, Debra A.	Lease, Sarah A	Tilseth, Brent S
Collins, Diane E.	Levesque, Bernadette	Torres, Elaine Rica O
Cornelius, Katlyn J	Madbouly, Abeer	Tram, Kevin V
Dees, Andrew	Maiers, Martin J.	Turner, Debra E
DiPrima, Stephanie N.	Malmberg, Craig	Venero, Jennifer T.
Drexler, Rebecca J.	Mattila, Deborah S	Vierra-Green, Cynthia A.
Enyart, Elizabeth	Maus, Tamara J	Vogel, Jennifer J
Ewer, Amy E.	McDonald, Abby A	Wadsworth, Kimberly D
Ewer, Sharon C.	McDonell, David W.	Wakaruk, Bridget K
Flesch, Susan M.	Milius, Robert	Waldvogel, Stephanie L.
Flickinger, Gail H.	Miralles, Carolina M	Westin, Andrew J
Fonstad, Rachel K.	Mitchem, Elliott T	Wheeler, Ericka L
Freeman, John L	Mueller, Curt J	Williams, Eric P.
Freeman, Shawn M.	Navarro, Willis H	Wirth, Antone M.
Gee, Katherine A	Oakes, Jennifer K.	Yang, Chia L
Gibbens, Ying Y	O'Connor, Karen	Yarra, Venu G
Gomez, Wilmer A	Ogega, Gideon O	

# Development of Medical Technology for Contingency Response to Marrow Toxic Agents

Dennis L. Confer, M.D., National Marrow Donor Program



## Objective:

- Develop, test and mature the ability of the NMDP to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents

## Approach:

- Contingency preparedness through RITN
- Develop science and technology to facilitate the rapid identification of donors
- Conduct immunogenetic research in transplantation
- Perform observational and prospective clinical research in transplantation

## Accomplishments:

- Joined the National Alliance for Radiation Readiness-Public/Private Partnership for readiness (NARR)
- Manuscript describing the likelihood of finding a suitable HLA matched donor or cord blood unit on the NMDP Registry accepted for publication in the New England Journal of Medicine
- Received Best Case Study award at the annual meeting of the American Society of Histocompatibility and Immunogenetics for an analysis of DNA stability on dried blood spots and buccal swabs
- Received Best Abstract award at the annual BMT Tandem Meetings for an analysis of HLA matching in a cohort of >8000 myeloablative unrelated donor transplantations for acute and chronic leukemia
- Revised and released 26 electronic clinical data collection forms in the FormsNet system

## Impact/Transitions:

- Formalized RITN membership in the NARR
- Revised clinical data collection forms released to the CIBMTR Network to allow collection of contemporary practice data

